PRODUCT INFORMATION

DUODOPA®

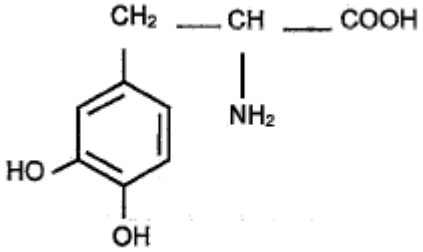
NAME OF THE MEDICINE

Non-proprietary Name

Levodopa
Carbidopa

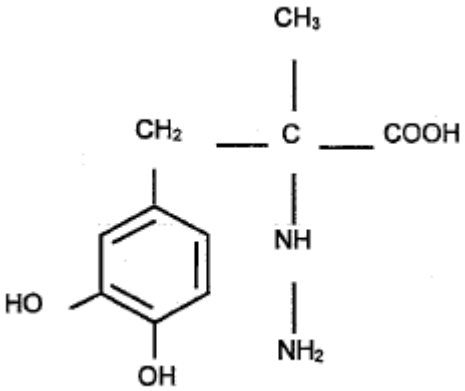
Chemical Structure

Levodopa



Mol. Wt: 197.2
Molecular Formula: $C_9H_{11}NO_4$
Chemical name: (2S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid

Carbidopa



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

Cas Number

Levodopa: 59-92-7
Carbidopa: 38821-49-7

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 for continuous intestinal infusion. 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.

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.

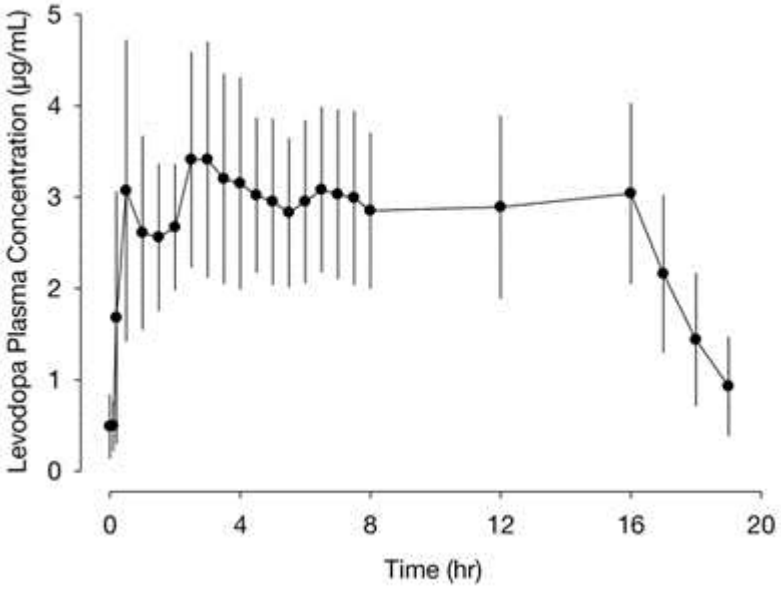
Pharmacokinetics

Absorption:

Levodopa is absorbed quickly and effectively from the intestine through a high capacity transport system for amino acids. A cross-study population pharmacokinetic analysis suggested that Duodopa has comparable levodopa bioavailability to the oral levodopa/carbidopa (100/25 mg tablets), when the combination intestinal gel is administered directly into the jejunum. The bioavailability estimate for levodopa from Duodopa relative to oral levodopa/carbidopa immediate release tablets was 97%. The absolute bioavailability of levodopa from oral levodopa/carbidopa immediate release tablets is reported to be 84-99%.

In the Duodopa Phase 1 study, intra-jejunal 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 and carbidopa plasma concentrations starting from hour-2 to hour-16 following initiation of infusion was low (CV=13% and 19%, respectively).

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



In the Duodopa double-blind, active-controlled, Phase 3 Study, the intra-subject variability in levodopa and carbidopa plasma concentrations were much lower for patients treated with Duodopa (CV=21% and 25%, respectively) than in patients treated with oral levodopa/carbidopa 100/25mg tablets (Sinemet® tablets over-encapsulated) (CV=67% and 39%, respectively).

Distribution:

Levodopa is co-administered with carbidopa, a decarboxylase inhibitor, which increases the bioavailability and decreases clearance for levodopa.

In patients on Duodopa with advanced Parkinson's disease, the model estimated the apparent steady-state volume of distribution (Vss/F) of levodopa was approximately 130 L for a 70 kg subject [10] or ~1.9L/kg, while the apparent clearance (CL/F) of levodopa, was 24.8 L/h when co-administered with carbidopa.
Levodopa has negligible binding to plasma proteins.

Carbidopa does not cross the blood-brain barrier.

Metabolism:

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. When administered with carbidopa, the elimination half-life of levodopa is approximately 1-2 hours. The elimination half-life of carbidopa is approximately 2 hours.

Carbidopa is metabolised to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid
Unchanged carbidopa accounts for 30% of the total urinary excretion of radioactive labelled oral carbidopa.

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

Early Stage Clinical Development Program

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 individualised 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: An open-label, randomised, 3+3 week crossover study in which 12 patients received Duodopa and controlled-release levodopa/carbidopa.
- NPP-001-92: An open-label study in which 7 patients who had been taking optimised 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.

Late Stage Clinical Development Program

This included two identically-designed Phase 3, 12-week, randomised, double-blind, double-dummy, active-controlled, parallel group, multicenter studies to evaluate the efficacy, safety, and tolerability of the Duodopa System. The studies were conducted with patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations despite optimised treatment with oral levodopa/carbidopa and other available anti-Parkinson's disease medications. The two studies were combined prior to breaking the blind and a single analysis was conducted.

Patients were eligible for participation in the studies if their response to anti-Parkinson's disease drug treatment was inadequate (i.e., they were experiencing ≥ 3 hours of “Off” time) and they demonstrated a clear responsiveness to treatment with levodopa. Seventy-one (71) patients enrolled in the study and 66 patients completed the treatment (3 patients discontinued treatment because of adverse events, 1 patient for lack of effect, and 1 patient for non-compliance).

Patients in this study had a mean age of 64.4 years and disease duration of 10.9 years.

Patients were randomised to 1 of 2 treatment arms: 1) Levodopa/carbidopa intestinal gel + placebo capsules, or 2) Placebo gel + levodopa/carbidopa capsules.

Duodopa or placebo gel was infused over 16 hours daily through a PEG-J tube using an ambulatory infusion pump. Patients in both treatment arms had a PEG-J device placement. Therefore, the primary difference between the treatment groups was the method of administration of levodopa/carbidopa (intestinal infusion versus oral capsule).

The primary outcome was a comparison between treatments in the change from baseline to week-12 in the total daily mean “Off” time based on Parkinson's Disease Diary© data using last observation carried forward. The "Off" time was normalised to a 16-hour awake period based on a typical person's waking day and the daily infusion duration of 16 hours.

The primary efficacy endpoint, change in normalised "Off" time (baseline to endpoint) demonstrated a statistically significant least square (LS) mean difference of -1.91 hours (P = 0.0015) in favour of the Duodopa treatment group (LS mean change: -4.04 hours for Duodopa group and -2.14 hours for active control group) (Table 2).

This change in “Off” time was associated with a statistically significant LS mean difference from baseline in the average daily normalised "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 randomisation and after 28 days of oral therapy standardisation.

Table 2. Change from Baseline to Endpoint in "Off" Time and in "On" Time Without Troublesome Dyskinesia

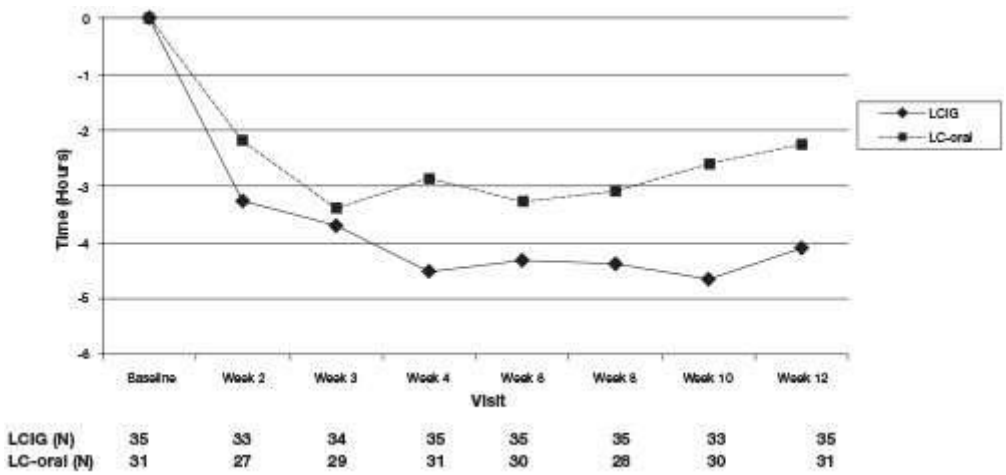
Treatment Group	N	Baseline Mean (SD) (hours)	Endpoint (SD) (hours)	LS Mean (SE) of Change (hours)	LS Mean (SE) of Difference (hours)	95% CI	*p* value
Primary Measure							
"Off" time Active Control[a]	31	6.90 (2.06)	4.95 (2.04)	-2.14 (0.66)	-1.91 (0.57)	(-3.05, -0.76)	0.0015
Duodopa	35	6.32 (1.72)	3.05 (2.52)	-4.04 (0.65)			
Secondary Measure							
"On" time without troublesome dyskinesia Active control	31	8.04 (2.09)	9.92 (2.62)	2.24 (0.76)	1.86 (0.65)	(0.56, 3.17)	0.0059
Duodopa	35	8.70 (2.01)	11.95 (2.67)	4.11 (0.75)			

SD = standard deviation; SE = standard error
[a] Active control, oral levodopa/carbidopa 100/25 mg tablets (Sinemet® tablets over-encapsulated)

Analyses also 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, Clinical Global Impression (CGI-I) score, and Unified Parkinson's Disease Rating Scale (UPDRS) Part II score (Activities of Daily Living). The PDQ-39 Summary Index-which showed a decrease from baseline of 10.9 points at week 12. Other secondary endpoints did not meet statistical significance based on the hierarchical testing procedure.

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 (Figure 2).

Figure 2. LS Mean Change in "Off" Time From Baseline to Each Post-Baseline Study Visit



The mean daily dose for the Duodopa group was 1117.3 (SD 473.3) mg/day levodopa in the Duodopa group and 1350.6 (SD 617.9) mg/day levodopa in the active control group. For 36 (97.3%) patients on Duodopa the mean daily rescue medication dose was 139.8 (81.3) mg/day levodopa and 180.6 (156.2)mg/day levodopa for the active control group.

A Phase 3, open-label, single-arm, multicentre 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 optimised treatment with available Parkinson's disease medications. The average daily normalised "Off" time changed by -4.44 hours from Baseline to Endpoint (6.77 hours at Baseline and 2.32 hours at Endpoint).

During the study, the number of patients who discontinued due to all reasons were 30/354 (8.5%) patients during the NJ test period and 52/354 (14.7%) during the Post PEG long-term treatment period. The mean duration of treatment was 329 days.

INDICATIONS

For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.

CONTRAINDICATIONS

Duodopa is contraindicated in patients with hypersensitivity to levodopa, carbidopa, or any of the excipients

Duodopa is contraindicated in patients with narrow-angle glaucoma.

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 hydrochloride) (see Interactions with other Medicines).

- Conditions in which adrenergics are contraindicated, eg. 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.
- Severe liver or renal insufficiency

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

- 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.
- 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 should be carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms (See Interactions with other Medicines).
- 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 during therapy.
- Levodopa has been associated with daytime 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 Precautions - 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.
- 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 or other factors, such as drugs used to treat Parkinson's. 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).
- 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.
- Reported complications in the clinical studies include bezoar, ileus, implant site erosion/ulcer, intestinal haemorrhage, intestinal ischemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumoperitoneum and post-operative wound infection. 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.
- 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.

Compulsive behaviour

There have been reports of patients experiencing intense urges to increased gambling, sexual urges, and shopping, eating, medication use and punding (repetitive purposeless activity), and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including Duodopa. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication stopped. Prescribers should ask the patient about the development of new or increased gambling urges, increased sexual urges or other intense urges while taking Duodopa. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Duodopa.

Hydrazine

Duodopa contains hydrazine, a degradation product of carbidopa that can be genotoxic and possibly carcinogenic. In non-clinical studies, hydrazine showed notable systemic toxicity, including hepatotoxicity and CNS toxicity, and is genotoxic as well as carcinogenic. Liver and lung tumours have been reported in rodent studies following oral administration of hydrazine. In rats, estimated exposure (plasma AUC) at tumourigenic doses was a 5-fold multiple of the anticipated human exposure associated with a daily dose of one DUODOPA cassette; the no-effect dose was associated with potential human exposure from one cassette. At higher DUODOPA doses, these margins will be reduced. The clinical significance of this hydrazine exposure is not known.

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.

Paediatric Use

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

Use in Elderly

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

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. See **Hydrazine** section

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. See **Hydrazine** section

INTERACTIONS WITH OTHER MEDICINES

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.

COMT inhibitors

Concomitant use of COMT (Catechol-O-Methyl-Transferase) inhibitors (eg entacapone) 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.

The mechanism of action of amantadine in Parkinson's disease is thought to be due to direct and indirect effects on dopamine neurons. Amantadine has also been shown to be a weak, non-competitive NMDA-receptor antagonist. Therefore, amantadine does not directly interact with or affect the bioavailability of levodopa

Levodopa forms a chelate with iron in the gastrointestinal tract leading to reduced absorption of levodopa.

As levodopa competes with certain amino acids for transport across the intestinal wall, the absorption of levodopa can be disturbed in patients who are on a protein rich diet.

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 effects that occur frequently with Duodopa include abdominal pain, complications of device insertion, dyskinesia, excessive granulation tissue, incision site erythema, nausea, postoperative wound infection, post procedural discharge, procedural pain, and procedural site reaction. Most of these adverse effects were reported early in studies, subsequent to the percutaneous endoscopic gastrostomy procedure, and occurred during the first 28 days.

Clinical Trials

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.

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 randomised, double-blind, double-dummy, active controlled study with 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.

Drug-related adverse reactions in patients who received Duodopa in all studies, regardless of the study design (double-blind or open-label) are presented in Table 3.

Table 3. Summary of Drug-Related Adverse Reactions (Excluding Procedure- and Device-Associated Adverse Reactions) in All Patients Who Received Duodopa

System Organ Class	MedDRA Preferred Term	Frequency[a]	Number of Subjects with Adverse Drug Reactions (N = 416) n (%)
Gastrointestinal disorders			
	Nausea	Very common	50 (12.0)
	Constipation	Common	41 (9.9)
	Vomiting	Common	28 (6.7)
	Abdominal distension	Common	19 (4.6)
	Dyspepsia	Common	15 (3.6)
	Flatulence	Common	13 (3.1)
	Diarrhoea	Common	11 (2.6)
	Dry mouth	Common	7 (1.7)
General disorders and administration site conditions			
	Fatigue	Common	6 (1.4)
	Pain	Common	6 (1.4)
Injury, poisoning and procedural complications			
	Fall	Common	27 (6.5)
Investigations			
	Weight decreased	Common	40 (9.6)
	Blood homocysteine increased	Common	29 (7.0)
	Vitamin B6 decreased	Common	28 (6.7)
	Amino acid level increased	Common	7 (1.7)
	Vitamin B12 decreased	Common	5 (1.2)

Metabolism and nutrition disorders			
	Decreased appetite	Common	16 (3.8)
	Vitamin B6 deficiency	Common	15 (3.6)
	Vitamin B12 deficiency	Common	6 (1.4)
	Hyperhomocysteinaemia	Common	5 (1.2)
Musculoskeletal and connective tissue disorders			
	Muscle spasms	Common	5 (1.2)
	Neck pain	Common	5 (1.2)
Nervous system disorders			
	Dyskinesia	Very common	42 (10.10
	Parkinson's disease	Common	33 (7.9)
	Polyneuropathy	Common	13 (3.1)
	Dizziness	Common	11 (2.6)
	Dystonia	Common	8 (1.9)
	On and off phenomenon	Common	8 (1.9)
	Paraesthesia	Common	8 (1.9)
	Syncope	Common	7 (1.7)
	Headache	Common	6 (1.4)
	Somnolence	Common	5 (1.2)
	Tremor	Common	5 (1.2)
Psychiatric disorders			
	Insomnia	Common	27 (6.5)
	Hallucination	Common	24 (5.8)
	Sleep attacks	Common	20 (4.8)
	Anxiety	Common	17 (4.1)
	Depression	Common	10 (2.4)
	Abnormal dreams	Common	7 (1.7)
	Confusional state	Common	7 (1.7)
	Sleep disorder	Common	7 (1.7)
	Agitation	Common	5 (1.2)
	Impulsive behaviour[b]	Common	5 (1.2)
	Psychotic disorder	Common	5 (1.2)
Respiratory, thoracic and mediastinal disorders			
	Oropharyngeal pain	Common	20 (4.8)
	Dyspnoea	Common	5 (1.2)
Skin and subcutaneous tissue disorders			
	Hyperhidrosis	Common	10 (2.4)
	Dermatitis contact	Common	5 (1.2)
Vascular disorders			
	Orthostatic hypotension	Common	21 (5.0)
	Hypotension	Common	7 (1.7)

[a] Very common (≥ 10%); common (≥ 1% and < 10%)
[b] 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.

Procedure-Related and Device-Related Adverse Reactions

An analysis was performed for patients who received Duodopa or placebo gel through a percutaneous endoscopic gastrostomy with jejunal tube (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).

Table 4. Summary of Procedure- and Device-Related Adverse Reactions in All Patients Who Received PEG-J

System Organ Class	MedDRA Preferred Term	Frequency[a]	Number of Subjects with Adverse Drug Reactions (N = 395) n (%)
Gastrointestinal disorders			
	Abdominal pain	Very common	125 (31.6)
	Pneumoperitoneum	Common	24 (6.1)
	Abdominal discomfort	Common	12 (3.0)
	Peritonitis	Common	12 (3.0)
	Abdominal pain upper	Common	8 (2.0)
General disorders and administration site conditions			
	Complications of device insertion	Very common	155 (39.2)
	Device dislocation	Common	9 (2.3)
	Device occlusion	Common	5 (1.3)
Infections and infestations			
	Postoperative wound infection	Very common	82 (20.8)
	Incision site cellulitis	Common	8 (2.0)
	Post procedural infection	Common	7 (1.8)
Injury, poisoning and procedural complications			
	Procedural pain	Very common	96 (24.3)
	Incision site erythema	Very common	67 (17.0)
	Procedural site reaction	Very common	46 (11.6)
	Post procedural discharge	Very common	43 (10.9)
	Incision site pain	Common	21 (5.3)
	Post procedural haemorrhage	Common	12 (3.0)
	Gastrointestinal stoma complication	Common	10 (2.5)
	Post procedural discomfort	Common	6 (1.5)
	Postoperative Ileus	Common	4 (1.0)
	Post procedural complication	Common	4 (1.0)
Skin and subcutaneous tissue disorders			
	Excessive granulation tissue	Very common	71 (18.0)

The device

Complication of device insertion was a commonly reported adverse reaction for both the nasojejunal tube (NJ) and the PEG-J. This adverse reaction was co-reported with one or more of the following adverse reactions for the NJ: oropharyngeal pain, abdominal distention, 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 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.

Complications with the devices are very common (≥1/10), e.g. connector leakage, dislocation of the intestinal tube. 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. There have been isolated reports of bezoar formation (see Precautions).

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

Procedure-related and device-related adverse reactions in this analysis set are presented in Table 4.

Laboratory values

The following laboratory abnormalities have been reported with levodopa/carbidopa: Elevated serum urea, alkaline phosphatases, AST (GOT), ALT (GPT), 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.

Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Polyneuropathy has been reported in patients treated with levodopa/carbidopa combinations, including Duodopa. In some of these patients, deficiencies of folic acid, vitamin B12 and vitamin B6 and elevated homocysteine have been observed; the etiology of these vitamin deficiencies is unclear. It is unknown whether there is a causal relationship between polyneuropathy and treatment with Duodopa or other levodopa/carbidopa combinations.

The following additional adverse reactions (presented in MedDRA preferred terms) have been identified during post-approval use of Duodopa in Parkinson's disease patients.

Blood and lymphatic system disorders: Agranulocytosis, Anaemia, Leukopenia, Thrombocytopenia

Immune system disorders: Anaphylactic reaction

Metabolism and nutritional disorders: Increased weight

Psychiatric disorders: Completed suicide, Suicide attempt, Nightmare, Euphoric mood, Dementia, Fear,
Abnormal thinking, Disorientation, Libido increased (see Precautions), Hypoaesthesia

Nervous system disorders: Ataxia, Gait disturbance, Convulsion

Eye disorders: Optic ischaemic neuropathy, Vision blurred, Blepharospasm, Diplopia, Angle closure glaucoma

Cardiac disorders: Palpitations, Heart rate irregular

Vascular disorders: Hypertension, Phlebitis

Respiratory, thoracic and mediastinal disorders: Dysphonia, Chest pain, Pneumonia aspiration, Respiration abnormal

Gastrointestinal disorders: Bezoar, Colitis ischemic, Gastric perforation, Gastrointestinal ischaemia, Gastrointestinal obstruction, Gastrointestinal perforation, Intussusception, Small intestinal haemorrhage, Small intestinal ischaemia, Small intestinal perforation, Small intestinal ulcer, Pancreatitis, Dysgeusia, Salivary hypersecretion, Dysphagia, Bruxism, Hiccups, Glossodynia

Skin and subcutaneous tissue disorders: Oedema, Urticaria, Pruritus, Erythema, Alopecia, Rash, Malignant melanoma (see Precautions)

Renal and urinary disorders: Chromaturia, Urinary retention, Urinary incontinence, Priapism

General disorders and administration site reactions: Asthenia, Malaise

The following additional adverse reactions (listed in MedDRA preferred terms) have been observed with dopaminergic drugs and could occur with Duodopa:

Blood and lymphatic system disorders: Haemolytic anaemia

Nervous system disorders: Trismus, Neuroleptic Malignant syndrome (see Precautions)

Eye disorders: Horner's syndrome, Mydriasis, Oculogyric crisis

Gastrointestinal disorders: Saliva discolouration

Skin and subcutaneous tissue disorders: Angioedema, Henoch-Schonlein purpure

DOSAGE AND ADMINISTRATION

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 (PEG-J) is placed. In cases where a physician considers this assessment is not necessary, the nasojejunal test phase may be waived and treatment initiated directly with placement of the PEG-J.

Duodopa is intended for continuous daytime intestinalinfusion. For long-term administration the gel should be infused with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy (PEG) with an outer transabdominal tube and an inner intestinal–tube, or via direct percutaneous endoscopic jejunostomy (PEJ) with a transabdominal tube. Alternatively a radiological gastrojejunostomy may be considered if PEG/direct PEJ is not suitable for any reason. Establishment of the transabdominal port and dose adjustments should be carried out in association with a neurological clinic.

The implantation placement target for the end of the tubing is the proximal small intestine past the Ligament of Treitz.

The dose should be adjusted to an optimal clinical response for the individual patient, which means 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. (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 should be used. Instructions for use of the portable pump are 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. The drug cassettes are for single use only and should not be used for longer than 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.

Morning dose: the morning dose is an individualised daily loading dose administered for between 10 and 30 minutes to achieve a therapeutic dose level.

Continuous maintenance dose: the Continuous Maintenance Dose (CMD) is administered after the Morning Dose and for the remainder of the 16-hour infusion period. When supplementary medicines are discontinued the Duodopa dose should be adjusted.

Extra bolus doses Extra doses of Duodopa can be used to assist in titration and during standard therapy to address immediate medical needs, such as the rapid deterioration of motor function. If the need for use of the extra dose feature exceeds five per day, the physician should increase the continuous maintenance dose. 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.

Table 5. Determination of Daily Doses (Morning, Continuous and Extra)

<table>
<tr><th></th><th>Morning Dose</th><th>Continuous Maintenance Dose (CMD)</th><th>Extra Doses</th></tr>
<tr><td>General</td><td>Usually 5 to 10 mL, corresponding to 100to 200 mg levodopa and should not exceed 15 mL (300 mg levodopa). The calculated morning dose should be increased to compensate for the priming of the deadspace.</td><td>May range from 1 to 10 mL/hour (20 to 200 mg levodopa/hour) and is usually 2 to 6 mL/hour (40 to 120 mg levodopa/hour). In exceptional cases a higher dose may be needed.</td><td>Usually 0.5 to 2.0 mL. In rare cases, a higher dose may be needed.
If the need for extra doses exceeds five per day, the physician should
increase the maintenance dose.</td></tr>
<tr><td>Initiation of Treatment (Day 1)</td><td>Patients should not be administered a full equivalent of their usual oral morning dose of levodopa/carbidopa. The morning dose of Duodopa is to be based on a percentage of the patient's usual morning oral levodopa/carbidopa dose.
<table><tr><td colspan="2">Morning dose of oral levodopa/carbidopa
vs. Percent of Dose Given as Duodopa</td></tr><tr><td>If the usual morning oral dose is</td><td>Give % Duodopa</td></tr><tr><td>0-200 mg</td><td>80%</td></tr><tr><td>201-399 mg</td><td>70%</td></tr><tr><td>≥ 400 mg</td><td>60%</td></tr></table></td><td>The CMD is adjustable in steps of 0.1 mL/hour (2 mg/hour).

Calculation:

Previous day’s dose minus
morning dose = A mg,

Divide A mg by 20 mg/mL = B mL

Divide B mL by 16 hours = C mL/hour

C x 0.9 = D mL/hour rate of infusion</td><td>May be given hourly, begin with 1 mL dose.</td></tr>
<tr><td>Day 2 to end of titration period (titration generally takes 4-7 days)</td><td>The morning dose may be adjusted as necessary based on the patient’s response to the previous day's morning dose.</td><td>Previous day's last infusion
rate.

The CMD is adjustable in steps of 0.1 mL/hour (2 mg/hour).</td><td>May be given hourly, begin with 1 mL dose.</td></tr>
<tr><td>Stable Daily Dose Period</td><td>Once the effective morning dose has been established, no further adjustments should be made.</td><td>Maintain previous day's last infusion rate.</td><td>May be given every 2 hours as needed (usually set between 0.5 to 2 mL per use).</td></tr>
</table>

[a] Usually by 3mL but amount may vary depending on tubing used.

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/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.

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

Dosage adjustment in renal and hepatic insufficiency

There are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic or renal impairment. Duodopa therapy should be administered cautiously to patients with severe renal or hepatic disease. Dosing with Duodopa is individualised by titration to optimal effect (which corresponds to individually optimised 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.

Handling of the pump and cassette

In the case of suspected or diagnosed dementia and lowered confusion threshold, the tube connections and patient's pump should be handled only by the nursing staff or an experienced caregiver.

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

OVERDOSAGE

Most prominent clinical symptoms of an overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasm can be an early sign of overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

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.

PRESENTATION AND STORAGE CONDITIONS

DUODOPA Intestinal Gel should be stored between 2 and 8°C.

Duodopa is stable for 24 months at -20˚C and 15 weeks at 5˚C. The product is only to be used for 16 hours once it is out of the refrigerator.

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

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

NAME AND ADDRESS OF THE SPONSOR

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AUSTRALIA
Tel: 1800 043 460

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine.

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

27 February 2008

DATE OF MOST RECENT AMENDMENT

05 January 2017

Version 12