PRODUCT MONOGRAPH

^{Pr}DUODOPA^{TM}

(levodopa/carbidopa intestinal gel)

Intestinal Gel (1 mL contains 20 mg levodopa and 5 mg carbidopa monohydrate)

Antiparkinson Agent

DUODOPA, for use in the treatment of advanced levodopa-responsive Parkinson's disease when satisfactory control of severe, disabling, motor fluctuations and hyper-/dyskinesia cannot be achieved with available combinations of Parkinson medicinal products, has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

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This product has been approved under the *Notice of Compliance with Conditions (NOC/c)* policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance be will be identified in the left margin by the symbol **NOC/c**. These sections may include, but are not limited to, the following:

Indications and Clinical Uses;

Action;

Warnings and Precautions;

Adverse Reactions;

Dosage and Administration; and

Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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^{Pr}DUODOPA^{TM}

(levodopa/carbidopa intestinal gel)

PART I: HEALTH PROFESSIONAL INFORMATION

DUODOPA, for use in the treatment of advanced levodopa-responsive Parkinson’s disease when satisfactory control of severe, disabling, motor fluctuations and hyper-/dyskinesia cannot be achieved with available combinations of Parkinson medicinal products, has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
Intestinal Gel	1 mL contains 20 mg levodopa and 5 mg carbidopa (monohydrate)	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

NOC/c

INDICATIONS AND CLINICAL USE

DUODOPA^{TM} (levodopa/carbidopa intestinal gel) may be useful for:

Treatment of advanced levodopa-responsive Parkinson's disease in which satisfactory control of severe, disabling motor fluctuations and hyper-/dyskinesia cannot be achieved with available combinations of Parkinson medicinal products.

DUODOPA is delivered by direct infusion to the upper small intestine (duodenum) by means of the portable, patient controlled CADD-Legacy DUODOPA pump, and requires insertion of a permanent access tube in the abdominal wall, by percutaneous endoscopic gastrostomy (PEG). Prior to insertion of the permanent PEG tube, a positive test of the clinical response to DUODOPA administered via a temporary nasoduodenal tube is recommended for all patients.

DUODOPA should only be prescribed by neurologists who meet the following requirements:

i) experience in treating patients with Parkinson's disease, and
ii) completion of the DUODOPA Education Program.

The DUODOPA Education Program is a risk mitigation program that is founded on the following core components that provide for the safe and effective use of DUODOPA in patients with advanced Parkinson's disease:

- **Implementation of a program to educate prescribing neurologists, surgeons and nurses about criteria for identification of suitable candidates for DUODOPA treatment (e.g., consideration of cognitive function, pre-existing GI conditions, feasibility of handling the device), surgical procedures required for use, appropriate postprocedural care including handling of complications associated with the device, and mode of drug administration.**
- **Distribution of educational materials for patients and caregivers that explain the product, percutaneous endoscopic gastrostomy procedure, proper use of the product, frequent complications associated with this mode of administration, how to manage complications (e.g., seek medical attention)(see ADVERSE REACTIONS), and rare, serious complications that may arise in connection with PEG tube placement (e.g. acute bleeding and damage to the pharynx-gullet-gastric mucosa associated with gastroscopy, peritonitis due to leakage of gastric fluid from the stroma and pneumonia).**

Geriatrics (> 65 years of age):
Levodopa/carbidopa has been used primarily in elderly patients. The recommendations in this product monograph reflect the clinical data derived from this experience.

Pediatrics:
The safety and efficacy of DUODOPA in patients under 18 years of age has not been established.

NOC/c

CONTRAINDICATIONS

CONTRAINDICATIONS for treatment with levodopa

DUODOPA (levodopa/carbidopa intestinal gel) is contraindicated in patients with:

- hypersensitivity to levodopa or carbidopa or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- narrow-angle glaucoma
- clinical or laboratory evidence of uncompensated cardiovascular, cerebrovascular, endocrine, renal, hepatic, hematologic or pulmonary disease.

In general, nonselective monoamine oxidase (MAO) inhibitors should not be given concomitantly with levodopa, and should be withdrawn at least two weeks before initiation of treatment with DUODOPA. As an exception, selegiline-HCl, at the recommended dose that maintains selectivity for MAO Type B, may be administered concomitantly with DUODOPA. Concomitant use of selegiline and levodopa-carbidopa has been associated

with serious orthostatic hypotension (see DRUG INTERACTIONS, MAO Inhibitors).

DUODOPA should not be given when administration of a sympathomimetic amine is contraindicated (e.g., epinephrine, norepinephrine, isoproterenol).

CONTRAINDICATIONS for PEG tube placement:
The placement of a PEG tube for DUODOPA treatment is contraindicated in patients with the following conditions:

- Pathological changes of the gastric wall
- Inability to bring the gastric wall and abdominal wall together
- Blood coagulation disorders
- Peritonitis
- Acute pancreatitis
- Paralytic ileus

Serious Warnings and Precautions

NOC/c **Treatment of Patients with Gastrointestinal Conditions**

Patients with a history of upper gastrointestinal problems or problems with intestinal absorption have not been systematically evaluated in clinical trials of DUODOPA (levodopa/carbidopa intestinal gel). Therefore, a test period of nasoduodenal delivery to determine treatment response, prior to insertion of a PEG tube, is particularly important for such patients (see INDICATIONS AND CLINICAL USES).

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

Sudden Onset of Sleep

Patients receiving treatment with levodopa and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including the driving of a car, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on levodopa, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs and should be specifically asked about factors that may increase the risk with DUODOPA such as concomitant medications or the presence of sleep disorders. Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking DUODOPA. If drowsiness or sudden onset of sleep should occur, patients should be informed to immediately contact their physician.

Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Currently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness.

NOC/c WARNINGS AND PRECAUTIONS

General

DUODOPA (levodopa/carbidopa intestinal gel) therapy should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions.

Neurologic

DUODOPA is not recommended or indicated for the treatment of intention tremor, Huntington's chorea, or drug induced extrapyramidal reactions.

DUODOPA should be administered cautiously to patients who have a history of seizures, conditions associated with seizure or who have a lowered seizure threshold.

Neuroleptic Malignant Syndrome: DUODOPA must not be withdrawn abruptly. A symptom complex resembling Neuroleptic Malignant Syndrome (NMS), including muscular rigidity, elevated body temperature, mental changes (e.g. agitation, confusion), altered consciousness, autonomic instability and elevated serum creatine phosphokinase has been reported in association with rapid dose reduction, withdrawal of or changes in antiparkinsonian therapy. Therefore, patients should be carefully observed when the dose of levodopa/carbidopa is abruptly reduced or discontinued, especially if the patient is receiving anti-psychotics. Should a combination of such symptoms occur, the patient should be kept under medical surveillance, hospitalized if necessary, and appropriate symptomatic treatment given. This may include resumption of therapy with DUODOPA after appropriate evaluation.

Gastrointestinal

(see CONTRAINDICATIONS, Serious WARNINGS AND PRECAUTIONS and WARNINGS AND PRECAUTIONS: DUODOPA Treatment and Device-Related Complications).

DUODOPA Treatment and Device-Related Complications

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.

A sudden or gradual worsening of bradykinesia may indicate an obstruction in the device for whatever reason and needs to be explored.

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.

Skin
Some epidemiological studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. DUODOPA is one of the drugs used to treat Parkinson's disease. Although DUODOPA has not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients treated with DUODOPA should be made aware of these results and should undergo periodic dermatologic screening.

The following additional precautions are listed alphabetically.

Cardiovascular
DUODOPA therapy should be administered cautiously to patients with severe cardiovascular disease.

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

DUODOPA may induce orthostatic hypotension. Therefore DUODOPA should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

Ophthalmologic
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.

Peri-Operative Considerations
Except in emergencies, DUODOPA should, whenever possible, be discontinued 2-3 hours before surgical interventions requiring general anesthesia, as fluctuations in blood pressure and/or arrhythmias may occur in patients being treated with DUODOPA who undergo anesthesia with halothane. Therapy with DUODOPA may be resumed following surgery at pre-operative doses as soon as oral intake of fluid is allowed.

Psychiatric
All patients treated with DUODOPA should be monitored carefully for the development of mental changes, including depression with suicidal tendencies.

Patients with past or current psychosis should be treated with caution.

Psychomotor Performance

Levodopa and carbidopa may cause dizziness and symptomatic orthostatism (see WARNINGS AND PRECAUTIONS: Cardiovascular). 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 WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions).

Special Populations

Pregnant Women:

There are insufficient data about the use of levodopa/carbidopa in pregnant women. Data from animal studies have shown that levodopa and combinations of carbidopa and levodopa caused visceral and skeletal malformations in rabbits, but the potential risk to humans is not known (see TOXICOLOGY: Reproductive and Developmental Toxicity). DUODOPA should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the fetus.

Nursing Women:

Levodopa is excreted in the breast milk in significant quantities. There is evidence that lactation is suppressed during treatment with levodopa. Carbidopa is excreted in milk in animals but it is not known whether it is excreted in human breast milk. The safety of levodopa and carbidopa in the infant is not known. While using DUODOPA women should not breast feed.

Pediatrics:

The safety of levodopa and carbidopa in patients under 18 years of age has not been established

Geriatrics (> 65 years of age):

There are no special warnings/precautions for use in elderly patients.

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

With respect to the drug, the adverse event profile of DUODOPA (levodopa/carbidopa intestinal gel) is similar to that of oral levodopa/carbidopa. No unexpected tolerability or safety concerns, related to the drug, were reported in the clinical study program. Adverse events that occur frequently with levodopa/carbidopa are those due to pharmacological activity of dopamine (e.g.,abnormal involuntary movements, dyskinesias, somnolence, gastrointestinal disturbances, psychiatric disturbances). These reactions can usually be diminished by dosage reduction.

The need for percutaneous endoscopic gastrostomy (PEG) surgery for insertion of a permanent catheter into the duodenum leads to transient complications of stoma infection and abdominal

pain, which subside with proper care. Dislocation and occlusion of the intraduodenal catheter are common problems that require medical attention. In patients who have been treated with DUODOPA, adverse reactions related to the PEG tube have been reported at various times during treatment and were not limited to a specific time during the treatment period.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reactions

In Phase II and Phase III clinical trials there were 46 patients treated with DUODOPA. The most commonly reported adverse events during clinical trials with DUODOPA were similar to those reported by patients on oral levodopa/carbidopa. See Table 1 and Table 2 for the most commonly reported adverse events in DUODOPA pivotal clinical trials. The number of patients included in DUODOPA. clinical trials was insufficient to identify rare adverse events that are known to occur with levodopa Table 4 lists rare/very rare adverse events that have been reported with the use of oral levodopa/carbidopa during postmarketing experience.

Serious adverse events that have been reported with oral levodopa treatment include psychiatric disorders (e.g., psychotic episodes, depression with or without development of suidical tendencies) and cardiovascular effects. In the Phase II and Phase III DUODOPA clinical trials serious adverse events included atrial fibrillation (n=1), insomnia and confusion (n=1) and deterioration of depression (n=1) during DUODOPA treatment and brain concussion and syncope (n=1) during treatment with conventional medication. Of these serious adverse events, only the insomnia and confusion was determined to be linked to the medication.

During the Phase II and Phase III DUODOPA clinical trials, none of the patient discontinuations were considered drug-related. A retrospective analysis of medical records for all patients treated with DUODOPA (n=65) for up to approximately 11 years (average duration of approximately 3.7 years) indicated that twelve patients discontinued treatment with DUODOPA for reasons other than death. Reasons for discontinuation included: worsening (end-stage) of the disease (with motor and/or mental deterioration and inability to handle the device n=6), recurring problems with the intestinal tube or stoma (n=5) or concurrent disease (n=1).

There were no deaths in the Phase II and Phase III clinical trials. In the retrospective analysis, 7 deaths were reported. Causes of death included aspiration resulting in pneumonia or anoxia (n=5), heart attack (n=1) and stroke (n=1).

Table 1. Incidence of treatment emergent adverse events in Study NPP-001-99[a]

Adverse Event*	Sinemet n=16	DUODOPA n=12
	Number of patients	Number of patients
Anxiety	2	1
Constipation	4	3
Dizziness	2	2
Fall	2	2
Headache	2	3
Nausea	1	2
Insomnia	4	1
Abdominal pain-upper	2	0
Abnormal dreams	2	0

* MedDRA 9.1 terminology

[a] North American patients were not included. Therefore, adverse event rates may not be generalizable to this demographic area.

Table 2. Incidence of treatment emergent adverse events in Study NPP-001-02 [a]

Adverse Event*	Conventional anti-parkinsonian medications[b] n=21	DUODOPA n=24
	Number of patients	Number of patients
Dizziness	2	0
Dyskinesia	4	1
Dystonia	3	0
Headache	2	2
Hyperkinesia	3	3
Anorexia	0	2
Constipation	6	2
Diarrhoea	1	2
Palpitation	3	1
Hyperhydrosis	1	2
Agitation	2	2
Anxiety	3	3
Confusional state	0	2
Depression	5	3
Insomnia	5	1
Accident	0	2

* MedDRA 9.1 terminology

[a] North American patients were not included. Therefore, adverse event rates may not be generalizable to this demographic area.

[b] Conventional antiparkinsonian medications included levodopa/dopa-decarboxylase inhibitor often used in combination with other dopamine enhancing treatments.

Device-related Adverse Events

The majority of patients treated with DUODOPA in Phase II and Phase III clinical trials received nasoduodenal infusions of DUODOPA for approximately 3 to 4 weeks (see CLINICAL TRIALS). During these studies the most common adverse events related to the device and delivery of DUODOPA was dislocation of the intestinal tube. Ten patients decided not to continue with a permanent device after having tested DUODOPA nasoduodenally or via jejunostomy for 9 – 31 days.

The retrospective analysis of medical records from 58 patients who were treated with DUODOPA for periods ranging from a few days up to approximately 11 years after PEG surgery indicated that the most common device-related complications were related to the intestinal tube. The most frequently reported intestinal tube complications were dislocation of the tube (65%), occlusion of tube (36%) and kink/knot in tube (19%). The most frequently reported adverse events related to the stoma included secretion from stoma (33%), infection of stoma (28%), proud flesh (raised granular tissue) around stoma (15.5%) and pain around stoma (9%). Complications related to the device were reported at various times during treatment and were not limited to a specific time during the treatment period. Initially the rate of PEG-related complications was low. With longer-term treatment, complications relating to the PEG become more prevalent (mainly loose connectors and leakage) (Table 3).

Table 3: Frequency of reported technical problems in the retrospective study (NPP-002-02) Patients treated with Duodopa via PEG for at least 6 months (N=50)*

Year 1	**Pump**	**Intestinal tube**	**Stoma**	**PEG tube**
Number and percentage of patients with problem	8 (16%)	34 (68%)	18 (36%)	3 (6%)
Number of times per patient	1-2	1-8	1-4	1-2
Average number of times per patient with problem	1	2.7	1.5	2.3
Total follow-up				
Number and percentage of patients with problem	12 (24%)	47 (94%)	16 (32%)	29 (58%)
Number of times per patient	1-3	1-12	1-5	1-3
Average number of times per patient with problem	2	4.1	2.4	1.6

*North American patients were not included. Therefore, adverse event rates may not be generalizable to this demographic area.

Management of Device-Related Adverse Reactions

Occlusion, kinks or knots, of the intestinal tube lead to high pressure signals from the pump. Occlusions are usually remedied by flushing the tube with tap water; kinking may need readjustment of the tubing.

- 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). Relocation of the tube is done using a guide-wire to steer the tube into the duodenum under fluoroscopy.
- 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, but abdominal pain, infection and leakage of gastric fluid may occur. Reported complications include wound infection (the most common complaint) and peritonitis. Local infections around the stoma are treated conservatively (disinfectant); treatment with antibiotics is rarely needed.

Post-Market Spontaneous Adverse Event Reports for Oral Levodopa

With regard to drug-related adverse reactions the adverse event profile of DUODOPA is similar to that of oral levodopa. Table 4 is based on post-marketing adverse event reports for oral levodopa.

Table 4. Post-Market Spontaneous Adverse Event Reports for Oral Levodopa

MedDRA system organ class	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000 incl. isolated reports
Blood and lymphatic system disorders			Leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia	Agranulocytosis
Metabolism and nutrition disorders	Anorexia	Loss of weight, increased weight		
Psychiatric disorders	Hallucinations, confusion, nightmares, sleepiness, fatigue, sleeplessness, depression euphoria, dementia, psychotic episodes, agitation		fear, thinking reduced, disorientation, increased libido, numbness	Suicide attempts
Nervous system disorders	Dyskinesias, choreatic movements and dystonia, "ON-OFF" episodes, dizziness, bradykinesia ("ON-OFF" episodes)[1], somnolence[2]	Ataxia, increased tremor (of the hands)	Neuroleptic malignant syndrome, paraesthesias, falling, gait disturbance, 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, inclination to fainting, syncope			

Table 4. Post-Market Spontaneous Adverse Event Reports for Oral Levodopa

MedDRA system organ class	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000 incl. isolated reports
Vascular disorders	Orthostatic hypotension,	Hypertension	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Hoarseness, chest pain	Dyspnoea, abnormal breathing pattern	
Gastrointestinal disorders	Nausea, vomiting dry mouth, bitter taste	Constipation, diarrhea, sialorrhoea. Dysphagia, flatulence	Dyspepsia, gastrointestinal pain, dark saliva, bruxism, hiccups, gastrointestinal bleeding, burning sensation of the tongue, duodenal ulceration	
Skin and subcutaneous tissue disorders		Oedema	Angioedema, urticaria, pruritus, flushing, alopecia, exanthema, increased perspiration, dark-colored sweating, Schönlein-Henoch purpura	
Musculoskeletal, connective tissue and bone disorders		Muscle spasms		
Renal and urinary disorders		Dark urine	Urinary retention, urinary incontinence, priapism	
General disorders and administration site reactions		Weakness, malaise		

[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 (see **Serious WARNINGS AND PRECAUTIONS**)

Pathological (compulsive) gambling

Pathological (compulsive) gambling has been reported in post-market data, including those in the literature, for antiparkinson drugs. Sporadic cases of pathological (compulsive) gambling have been reported in patients treated with dopaminergic agents, including levodopa. Dosage adjustment should be considered in the management of this behaviour.

Abnormal Hematologic and Clinical Chemistry Findings

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 Coomb's test, and lowered values of haemoglobin and haematocrit.

Leucocytes, bacteria and blood in the urine have been reported.

DRUG INTERACTIONS

Overview

No specific pharmacokinetic studies have been conducted with DUODOPA (levodopa/carbidopa intestinal gel) and concomitant drugs. However, levodopa/carbidopa combinations have been used widely in clinical trials and clinical practice concomitantly with other drugs.

Drug-Drug Interactions

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 is added to the treatment of patients already receiving anti-hypertensives. DUODOPA should be administered cautiously and blood pressure should be monitored in patients receiving antihypertensive medication. Dosage adjustment of the antihypertensive agent may be required.

Tricyclic 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.

MAO inhibitors

See CONTRAINDICATIONS

In general, nonselective monoamine oxidase (MAO) inhibitors should not be given concomitantly with levodopa, and should be withdrawn at least two weeks before initiation of treatment with DUODOPA. DUODOPA may be administered concomitantly with the recommended dose of selegiline-HCl, which is selective for MAO type B (See CONTRAINDICATIONS). However, concomitant use of selegiline and levodopa-carbidopa has been associated with serious orthostatic hypotension.

Antipsychotics

Concomitant administration of antipsychotics with dopamine receptor blocking properties, particularly D_2 receptor antagonists (e.g., phenothiazines, butyrophenones and risperidone), may reduce the therapeutic effects of levodopa and should be used with caution. Patients should be carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms.

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.

Other drugs that may reduce therapeutic response to levodopa

Dopamine receptor antagonists (some antipsychotics, e.g. phenothiazines, butyrophenones and risperidone and some antiemetics, e.g. metoclopramide) may decrease the effects of levodopa. Benzodiazepines, isoniazid, phenytoin and papaverine can also reduce the therapeutic effect of levodopa. Patients taking these medications together with DUODOPA, should be observed carefully for loss of therapeutic response.

Anesthetics

Except in emergencies, DUODOPA should, whenever possible, be discontinued 2-3 hours before surgical intervention requiring general anesthesia, as fluctuations in blood pressure and/or arrhythmias may occur in patients being treated with DUODOPA who undergo anesthesia with halothane. DUODOPA treatment may be resumed at pre-operative doses as soon as oral intake of fluid is allowed.

Other antiparkinsonian drugs

When used in combination with other anti-parkinsonian agents (anticholinergics, amantadine, dopamine agonists) the desired and undesired effects of treatment may be intensified. It may be necessary to reduce the dosage of DUODOPA or the other substance.

Concomitant use of COMT (Catechol-*O*-Methyl Transferase) inhibitors and DUODOPA can increase the bioavailability of levodopa and the dose of DUODOPA may need adjustment.

Amantadine has a synergistic effect with levodopa and may increase levodopa related adverse events. An adjustment of the dose of DUODOPA may be needed.

Sympathomimetics

DUODOPA should not be administered concomitantly with sympathomimetic agents, which stimulate the sympathetic nervous system (e.g., epinephrine, norepinephrine, isoproterenol or amphetamine) as levodopa may potentiate cardiovascular effects (See CONTRAINDICATIONS). If concomitant administration is necessary, close surveillance of the cardiovascular system is essential, and the dose of the sympathomimetic agents may need to be reduced.

Iron
Levodopa may form a chelate with iron (drug-iron complex) in the gastrointestinal tract leading to reduced absorption of levodopa. Therefore, iron supplements and iron-containing multivitamins can decrease the bioavailability of levodopa.

Drug-Food Interactions
As levodopa is competitive with certain amino acids, the absorption of levodopa and its transport across the blood-brain barrier can be impaired. Therefore, its therapeutic effects may be diminished in patients who are on a protein rich diet.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
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.

DOSAGE AND ADMINISTRATION

NOC/c

DUODOPA (levodopa/carbidopa intestinal gel) should only be prescribed by neurologists who meet the following requirements:

i. **experience in treating patients with Parkinson's disease, and**
ii. **completion of the DUODOPA Education Program.**

The DUODOPA Education Program is a risk mitigation program that is founded on the following core components that provide for the safe and effective use of DUODOPA in patients with advanced Parkinson's disease:

- **Implementation of a program to educate prescribing neurologists, surgeons and nurses about criteria for identification of suitable candidates for DUODOPA treatment (e.g., consideration of cognitive function, pre-existing GI conditions, feasibility of handling the device), surgical procedures required for use, appropriate postprocedural care including handling of complications associated with the device, and mode of drug administration.**
- **Distribution of educational materials for patients and caregivers that explain the product, percutaneous endoscopic gastrostomy procedure, proper use of the product, frequent complications associated with this mode of administration, how to manage complications (e.g., seek medical attention)(see ADVERSE REACTIONS), and rare, serious complications that may arise in connection with PEG tube placement (e.g. acute bleeding and damage to the pharynx-gullet-gastric mucosa associated with gastroscopy, peritonitis due to leakage of gastric fluid from the stoma and pneumonia).**

Dosing Considerations

General

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

Mode of administration

DUODOPA is a gel for continuous administration to the small intestine. A temporary nasoduodenal tube is recommended for a test period of at least 3 days duration to determine if the patient responds favourably to this method of treatment and to optimize the dose, prior to insertion of a permanent intestinal tube by percutaneous endoscopic gastrosotomy.

Long-term administration of DUODOPA, requires insertion of a permanent outer transabdominal tube and inner intestinal tube by percutaneous endoscopic gastrostomy, which enables direct delivery of the gel into the duodenum with a portable pump. Radiological gastrojejunostomy may be considered for insertion of the permanent tube if percutaneous endoscopic gastrostomy is not suitable for any reason (e.g., in patients with esophageal obstruction or stricture).

Only the CADD-legacy DUODOPA pump should be used for administration of DUODOPA. A manual with instructions for using the portable pump is provided with the pump. In the case of suspected or diagnosed dementia and lowered confusion threshold, the pump should be handled only by trained nursing staff or caregivers.

Optimization of therapy and co-administration with other drugs
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-time episodes (bradykinesia) and minimizing ON-time with disabling dyskinesia (see Recommended Dose and Dosage Adjustment).

DUODOPA should be given initially as monotherapy. If required other medicinal products for Parkinson's disease can be taken concurrently (see DRUG INTERACTIONS).

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 WARNINGS AND PRECAUTIONS-Neuroleptic Malignant Syndrome).

Except in emergencies, if general anaesthesia is required, treatment with DUODOPA should, whenever possible, be discontinued 2-3 hours before. If therapy has to be stopped temporarily, DUODOPA may be resumed at pre-operative doses as soon as oral intake of fluid is allowed (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment
Levodopa given as DUODOPA has the same bioavailability as oral levodopa and therefore conversion from one form to another should be done in approximately a 1:1 ratio.
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. During the test period the patient is supplied with and trained in the use of the portable pump, and the three DUODOPA dosing parameters are individualized for the patient. The patient can then independently control the infusion rates to suit their daily requirements, within parameters pre-set under the direction of their physician.

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 accordingly. 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). 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 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.

In DUODOPA clinical trials extra bolus doses were permitted, during the day, as required to optimize treatment responses. In study NPP-001-99, during DUODOPA treatment and during oral levodopa treatment (as monotherapy or in combination with other antiparkinsonian medications), most patients (approximately three-quarters), required extra doses.

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. If medically justified DUODOPA may be administered during the night (e.g., nocturnal akinesia).

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.

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

Missed Dose
If the pump malfunctions, and dosing is interrupted, resume dosing as per the instructions above. Should complete failure of the intestinal tube or pump occur, the patient must be treated with oral levodopa/carbidopa until the problem is resolved.

Administration
The cassette containing DUODOPA should be attached to the portable pump and the system connected to the nasoduodenal tube or the transabdominal port/duodenal tube for administration just prior to use, according to the instructions provided in the pump instruction manual. The drug cassettes are for single use only and should not be used for longer than one day (up to 16 hours) even if some medicinal product remains. An opened cassette should not be re-used. By the end of the storage time (i.e., after 16 hours in use, or when approaching the expiration date) the gel might become slightly yellow. This does not influence the concentration of the drug or the treatment.

Substances other than DUODOPA should not be administered into the tube. There is a risk that objects (e.g., small tablet fragments or food particles) might block the intestinal tube.

OVERDOSAGE

Symptoms
The most prominent symptoms of an overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasm can be an early sign of overdose.

Treatment
The treatment of an acute overdose of DUODOPA (levodopa/carbidopa intestinal gel) 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.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
DUODOPA (levodopa/carbidopa intestinal gel) is a combination of levodopa and carbidopa (ratio 4:1) in a gel for continuous intestinal infusion in patients with advanced, levodopa-responsive Parkinson's disease who experience severe motor fluctuations and hyper-/dyskinesia, despite treatment with available combinations of Parkinson medicinal products.

Levodopa, a metabolic precursor of dopamine, is transported across the blood-brain barrier by the carrier for large neutral amino acids (LNAA) and relieves motor symptoms of Parkinson's disease following decarboxylation to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral or peripheral decarboxylation of levodopa, which means that a larger amount of unchanged 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 and large doses of levodopa result in high levels of circulating dopamine and other dopa metabolites. Excessive quantities of these substances formed in peripheral tissues may be partly responsible for some of the side effects of levodopa, such as nausea, vomiting and cardiac arrhythmias. Combined therapy with levodopa and carbidopa reduces the amount of levodopa required for optimum therapeutic benefit and the incidence of such side effects.

Therapy with DUODOPA allows continuous infusion of levodopa/carbidopa directly into the duodenum. With administration of levodopa/carbidopa directly into the duodenum, gastric emptying rate, which is often erratic in Parkinson’s disease patients and a contributing factor to the variation in plasma levodopa concentrations, has no influence on the absorption rate. Thus, intraduodenal infusion enables plasma concentrations of levodopa to be kept at a steady level within the individual therapeutic window, eliminating end-of-dose and peak plasma concentrations that occur with oral administration and contribute to motor fluctuations and dyskinesias.

Pharmacodynamics
The DUODOPA system serves to provide continuous rather than intermittent stimulation of the dopaminergic receptors in the brain by permitting plasma concentrations of levodopa to be kept within the individual's optimal therapeutic window. In the early phases of the disease, i.e. the first 3-4 years after diagnosis, such variability in plasma levodopa concentrations is of no consequence for the clinical response. However, after approximately 5 years of levodopa treatment, motor oscillations start to appear (Figure 1). The incidence of motor fluctuations and dyskinesias varies between 20 and 50% of the patients in different studies.

Progression of Parkinson's Disease

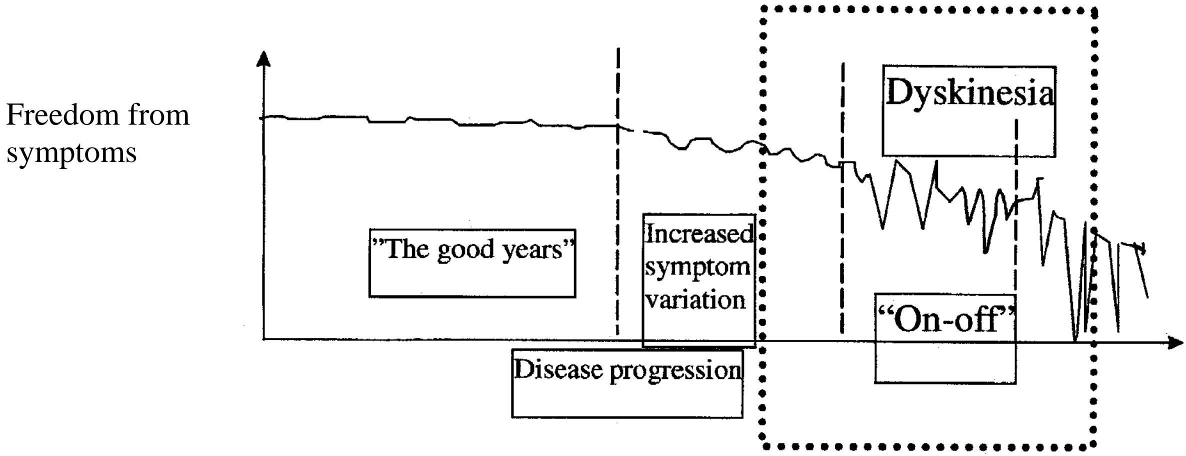

Figure 1: During the "good years" the cardinal symptoms of the disease (tremor, rigidity, slowness of movements (bradykinesia)) are improved by levodopa given orally 3-4 times daily. After some years, however, the patient starts to experience increased symptom variation that coincides with dose intake, "end-of-dose deterioration". In later stages of the disease, marked motor oscillations occur with "wearing off" (end-of-dose deterioration) and "on-off" phenomena and dyskinesias, i.e. hyperkinesias (involuntary, exaggerated chorea-like movements) or dystonia (abnormal muscular contractions that distorts movements).

The response oscillations and dyskinesias after oral intake of levodopa may be explained by an underlying progression of the disease with gradual disappearance of dopaminergic neurons in the brain. When approaching a certain threshold of degeneration of dopamine containing (and other) neurons and consequently, a reduction in the capacity to store dopamine in the brain tissue, the response to levodopa becomes increasingly unstable. It has therefore been hypothesized that the therapeutic plasma levodopa concentration window becomes increasingly narrow with time. Thus, an insufficient response (Parkinsonism) occurs when the levodopa concentration is below the window, and the dyskinesias occur when the concentration increases above an upper threshold for the individual. A schematic drawing of this concept is shown in Figure 2.

Instability of Levodopa Response During Progression of Parkinson's Disease

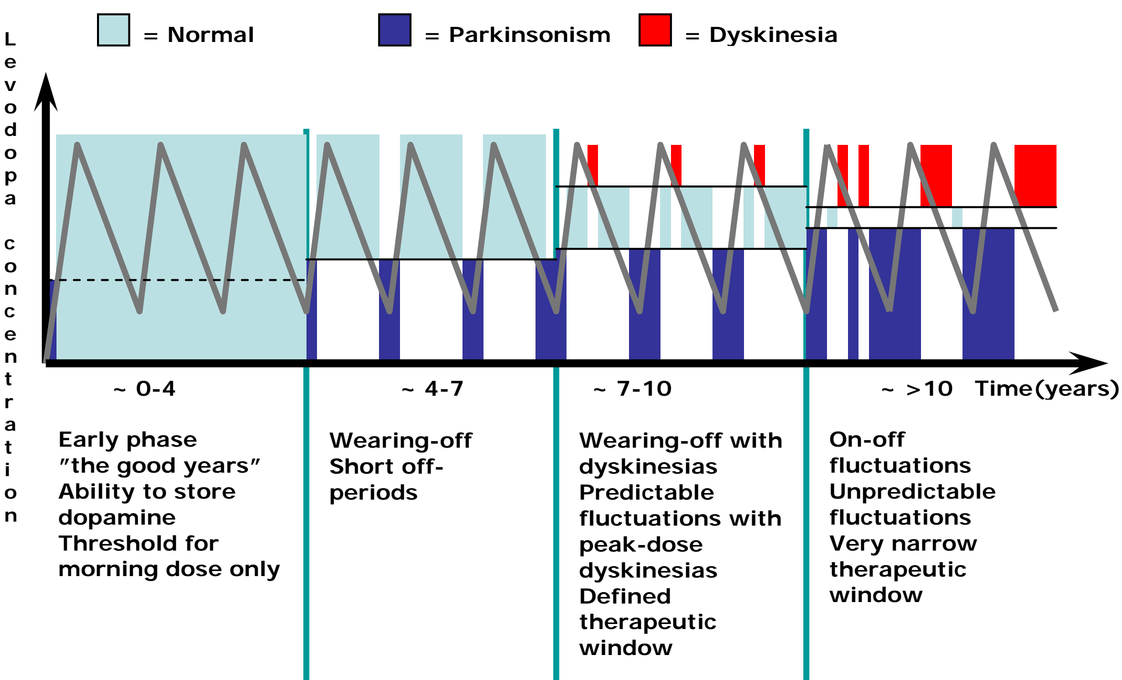

Figure 2. Schematic representation of the instability of the levodopa response during progression of Parkinson's disease. During the "good years" the therapeutic response is sufficient above a certain minimal plasma levodopa concentration. "Wearing off" (end-of-dose deterioration) starts to appear between ~4-and 7 years, when the levodopa levels decrease below a lower threshold for response. Between ~7 and 10 years, episodes of dyskinesia accompany peak concentrations, and longer "off"-periods start to appear. A few years later the therapeutic plasma concentration window becomes even narrower.

Although various approaches are used to manage the increasingly unstable levodopa response. some patients continue to experience unacceptable outcomes with regard to motor fluctuations and dyskinesias. Clinical trials with DUODOPA demonstrated that intraduodenal delivery of levodopa/carbidopa resulted in less intraindividual variation in plasma levodopa concentrations, less motor fluctuations and less dykinesias (see CLINICAL TRIALS).

Pharmacokinetics

Pharmacokinetic-pharmacodynamic relationship

The reduced fluctuations in levodopa plasma concentrations correlate with decreased fluctuations in treatment response. The levodopa dose needed varies considerably among patients with 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. After a period of satisfactory treatment with DUODOPA, patients may find that a lower dose of levodopa will provide a satisfactory clinical response.

Absorption:

DUODOPA is administered *via* a tube inserted directly into the duodenum. Levodopa is absorbed quickly and effectively from the intestine through a high capacity transport system for amino acids. Levodopa given as DUODOPA has the same bioavailability as levodopa given orally as tablets (81-98%). The variation in intraindividual levodopa plasma concentration is

considerably smaller for DUODOPA than for orally administered levodopa/decarboxylase inhibitor because gastric emptying rate has no influence on the absorption rate of levodopa when it is given by continuous intestinal administration. With an initial high morning dose of DUODOPA the therapeutic plasma level of levodopa is reached within 10-30 minutes.

As levodopa is competitive with certain amino acids, the absorption of levodopa and its transport across the blood-brain barrier can be impaired. Therefore, its therapeutic effects may be diminished in patients who are on a protein rich diet.

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 erythocytes and plasma is about 1 and levodopa has a negligible binding to plasma proteins.

Metabolism:
Levodopa is metabolized by two major pathways (decarboxylation and O-methylation) and two minor pathways (transamination and oxidation).

Decarboxylation of levodopa to dopamine by aromatic amino acid decarboxylase (AAAD) is the predominant metabolic pathway for levodopa administered without an inhibitor of AAAD. This enzyme is widely distributed in the body, with high activity in the intestinal wall, liver, kidney brain and white blood cells.The major metabolites of this pathway are homovanillic acid and dihydroxyphenylacetic acid.

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. COMT methylates levodopa to 3-O-methyldopa. The half-life of this metabolite is approximately ten times longer than that of levodopa. This is due to a significantly lower clearance which then results in significantly higher plasma concentration of this metabolite after chronic dosing.

Carbidopa is metabolized into 6 metabolites. The major metabolic pathway for carbidopa is dehydrazination but no hydrazine was detected. This result indicates that carbidopa may be oxidized by metabolic enzymes to hydrocarbon and free N_2.

Excretion:
After intravenous administration of levodopa, together with carbidopa, the plasma clearance is 0.3 L/h/kg. The elimination half-life for levodopa is approximately 1-2 hours (in the presence of a dopa-decarboxylase inhibitor). Levodopa is eliminated completely through metabolism and the metabolites formed are excreted mainly in the urine..

In humans, approximately 50% of an oral dose of carbidopa is excreted in the urine.

Special Populations and Conditions
No specific pharmacokinetic studies were conducted in special populations.

STORAGE AND STABILITY

Store in a refrigerator (2°C-8°C). The cassette should be kept in the outer carton in order to protect from light.

SPECIAL HANDLING INSTRUCTIONS

Empty/used cassettes should be returned to the pharmacy for destruction.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DUODOPA is an intestinal gel, white to slightly yellow in colour, for continuous intestinal administration. Each mL of DUODOPA contains 20 mg levodopa and 5 mg carbidopa (monohydrate).

100 mL of DUODOPA is contained in a PVC bag, which is in turn kept inside a hard plastic cassette for protection. Each carton of DUODOPA contains 7 cassettes.

Non-medicinal Ingredients: Carmellose sodium and purified water.

PART II: SCIENTIFIC INFORMATION

DUODOPA, for use in the treatment of advanced levodopa-responsive Parkinson's disease when satisfactory control of severe, disabling, motor fluctuations and hyper-/dyskinesia cannot be achieved with available combinations of Parkinson medicinal products, has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

PHARMACEUTICAL INFORMATION

Drug Substance

LEVODOPA	CARBIDOPA
Proper name: Levodopa	Proper name: Carbidopa
Chemical name: (2*S*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid	Chemical name: (2*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid, monohydrate
Molecular formula: $C_9H_{11}NO_4$ Molecular weight: 192.7	Molecular formula: $C_{10}H_{14}N_2O_4 \cdot H_2O$ Molecular weight: 244.24
Structural formula: Levodopa	Structural formula: Carbidopa
Physicochemical properties: An aromatic amino acid White or slightly cream-coloured, crystalline powder Slightly soluble in water, practically Insoluble in alcohol and ether. Freely soluble in 1M HCl, sparingly soluble in 0.1 M HCl. Light and oxygen sensitive	Physicochemical properties: An inhibitor of aromatic amino acid decarboxylase 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. Light and oxygen sensitive

NOC/c CLINICAL TRIALS

There were 46 patients included in Phase II and Phase III trials (pivotal and non-pivotal). Treatment durations and comparator treatments varied with studies. Study NPP-001-99 was 3+3 week (3 weeks DUODOPA + 3 weeks SINEMET), NPP-001-92 was a 6-month study and NPP-001-02 was a 3+3 week study (3 weeks DUODOPA + 3 weeks conventional anti-PD). Efficacy assessments in the studies included determinations of plasma levodopa concentrations, PLM (posture, locomotion, manual dexterity) test and video scoring of motor function. Other efficacy assessment scales used were the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr Scale.

All studies were open label with the exception of a study that was discontinued after enrollment of 5 patients. Assessments of motor fluctuation and dyskinesias from video recordings were blinded in NPP-001-02, but were not blinded in NPP-001-92 and NPP-001-99. Determinations of plasma levodopa concentrations and the automated and computerized PLM test were single blind.

Patients included in the DUODOPA (levodopa/carbidopa intestinal gel) clinical studies were usually above 50 years of age (age range: 39-79 years). Their duration of illness ranged from 2 to 31 years, they had been on levodopa treatment for 4-21 years or more, and they had suffered from motor fluctuations for 3-17 years in spite of many permutations of treatment with levodopa/carbidopa in combination with other antiparkinson drugs (COMT inhibitors, dopamine agonists, anticholinergics). Their stage of disease according to Hoehn and Yahr "at worst" was 2-5 on a 5-point scale. The majority of patients had a Hoehn & Yahr 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. As such, the patients matched the target indication for treatment with DUODOPA.

Pivotal trials

Table 5. Patient demographics and trial design for DUODOPA pivotal trials.

Study No.	Design	Subjects	Diagnosis & Inclusion Criteria	Duration	Test Products/Dosage/ Route of Administration	Endpoints
NPP-001-99 (1999-2000)	Open label, cross-over, single centre, PK study comparing DUODOPA nasoduodenal infusion vs oral levodopa/carbidopa tablets (SINEMET)*	-N=12 -M/F: 10/2 -Age: 39-76 yrs -PD dx : 8-29 yrs -levodopa tx : 3-26 yrs	Advanced idiopathic, levodopa-responsive PD with diurnal motor fluctuations despite optimized oral levodopa tx.	3 weeks DUODOPA[a] + 3 weeks SINEMET[a]	DUODOPA by nasoduodenal infusion Individually adjusted infusion rates 46-116 mg levodopa/hour (between 6 am and 10 pm); -range of morning bolus doses: 100 – 300 mg -mean total daily doses levodopa: 945 to 2694 mg Sinemet Depot Mite/Sinemet p.o.; individually adjusted doses -mean daily doses: 850-2933 mg levodopa	Primary efficacy endpoint: -Plasma levodopa variance Secondary efficacy endpoints: -Number, duration and/or intensity of “off” and “hyperkinetic” periods (PLM-test and video scoring) -UPDRS and Schwab and England ADL scales -Hoehn and Yahr staging
NPP-001-02 (2002-2003)	Open label, cross-over study comparing DUODOPA nasoduodenal infusion vs conventional anti-PD medication[a]	-N=24 -M/F: 18/6 -Age: 50-79 years -PD dx: 2-23 yrs -levodopa tx : 5-21 yrs	Advanced idiopathic levodopa-responsive PD with severe fluctuating response despite frequent administrations of oral levodopa	3 weeks DUODOPA[a] + 3 weeks conventional anti-PD medication	DUODOPA by intraduodenal infusion Individually adjusted infusion rates 26-196 mg levodopa/hour (between 6 am and 10 pm); -range of morning bolus doses: 20-200mg levodopa -mean extra bolus doses: 2-40 mg -mean total daily doses levodopa: 456 to 3556 mg Conventional anti-PD medication; individually adjusted doses -mean daily doses: 275 – 2400 mg levodopa in 19 hours.	Primary efficacy endpoint: -Blinded assessment of video scoring (Duration and/or intensity of “on”, “off” and “hyperkinetic” periods also assessed) Secondary efficacy endpoint: -UPDRS -Electronic home diary. Quality of life instruments: PDQ-39 and 15D.

[a]Co-administration of other antiparkinsonian medications was not permitted during this treatment period. Extra doses of levodopa were permitted as required.
[b]Conventional anti-PD medications included levodopa/dopa-decarboxylase inhibitor often used in combination with other dopamine enhancing treatments.

Table 6. Efficacy results from DUODOPA pivotal trials.

Study	N	Primary efficacy endpoint	Secondary efficacy endpoint
NPP-001-099	12	The primary efficacy endpoint was plasma levodopa variance[a]. Mean intraindividual plasma levodopa variance was significantly lower during intraduodenal treatment for each group (0.16 and 0.33) than during oral treatment (0.63 and 1.13); $p < 0.01$ for the estimated difference between treatments. Mean intraindividual coefficient of variation[b] was also significantly lower during intraduodenal treatment for each group (0.15 and 0.15) than during oral treatment (0.30 and 0.39), $p < 0.01$ for the estimated difference between treatments.	Several secondary outcome assessments in this study showed improvement with DUODOPA. These included more time spent in a 'normal motor state' assessed from unblinded patient video recordings, as well as improvements in motor function, activities of daily living, mood and behavior assessed by the UPDRS and Modified Schwab and England ADL scale.
NPP-001-02	24	The primary efficacy endpoint was the mean percentage of time ON (scored as the response interval -1 to +1 in blinded ratings of patient videos). The mean percentages OFF time and ON time with moderate to severe dyskinesia were also assessed. There was a statistically significant difference in favour of DUODOPA in the mean percentage time spent in the treatment response interval -1 to +1 (90.7% for DUODOPA vs 74.5% for conventional therapy, $p<0.01$). The increase in mean percentage time ON was accompanied by a statistically significant ($p<0.01$) and marked decrease in the mean percentage OFF time (or ON with Parkinsonism) to a very low level during DUODOPA treatment. The percentage of ON time with moderate to severe dyskinesia was not statistically different for the two treatments.	Statistically significant differences between the treatments in favour of DUODOPA were observed for the UPDRS total score. Treatment differences for Part 1 (mentation, behavior, mood) and Part 3 (motor examination) of the UPDRS were not statistically significant. The improvement during DUODOPA treatment relative to that during conventional medication was statistically significant in the two Quality of Life instruments, PDQ-39 and 15D.

[a] Plasma levodopa variance =(Standard deviation)^2. Results were based on data from the Full Analysis Set, which included all patients with at least 1 complete test day per treatment period (3 test days per treatment period).
[b] Coefficient of variation = Standard deviation/mean
[c] Results were based on data from the Intent to Treat population, which included all patients who received treatment.

The clinical trials showed that intraindividual plasma levodopa variance was reduced during DUODOPA treatment compared to optimized oral levodopa treatment. In addition, patients generally performed faster and had less motor fluctuations during DUODOPA treatment than during optimised oral treatment. Clinically and statistically significant improvements were observed based on video scoring and PLM-tests showing increase in percentage time ON and decreases in percentage time OFF, UPDRS results and the patients' perceived benefit from DUODOPA documented by quality of life instruments and electronic home diary.

Non-pivotal trial

NNP-001-92
This study compared the mean movement time (MT) calculated from the automated and computerized PLM (posture, locomotion, manual dexterity) test in 7 patients treated for 1 month with oral levodopa/carbidopa and 6 months with DUODOPA infusion after PEG surgery. The results indicated that MT decreased significantly (p=0.05) after 6 months of DUODOPA treatment relative to MT measured after 1 month of oral levodopa/carbidopa. Variances in MT also decreased on infusion compared to oral therapy (p=0.001). Unblinded ratings of video films supported PLM test results, as the patients spent more time in "normal" motoric state on infusion, and less time in "off" and "hyperkinetic" states compared to during oral therapy.

Restrospective analyses

NPP-002-00
NPP-002-00 was a retrospective analysis of medical records from patients treated with DUODOPA from January 1991 to December 1999 (n=31), assessing duration of DUODOPA treatment and discontinuation from treatment. Treatment time ranged from 15 days to approximately 8.5 years (median duration of approximately 3.7 years.

For the nine patients who stopped DUODOPA therapy duration of treatment ranged from 15 days to 5.4 years. For 6 of the 9 patients who discontinued treatment, complications associated with the infusion system or intestinal tube were reported among reasons for discontinuation. Other reasons for discontinuation included gastric pain, repeated pneumonia, dementia, and development of Parkinson's plus syndrome.

Technical problems leading to treatment interruptions ocurred in less than half of the patients (14 out of 31). The most common technical problem was dislocation of the tip of the tube from the duodenum into the stomach.

NPP-002-02
NPP-002-02 was a retrospective analysis of medical records from patients treated with DUODOPA from January 1991 to June 2002 (n=65)[1], assessing the safety of DUODOPA during long-term treatment. Among the 65 patients included in the analysis, 58 patients underwent PEG surgery for long-term treatment with DUODOPA. Fifty-two patients were treated for at least 12 months with a mean duration of 4.1 years (range 1-10.7) and 215 patient-years of exposure.

Twenty-nine patients discontinued treatment with DUODOPA for reasons that included death (n=7), worsening of disease in combination with adverse events related to the infusion system or concurrent disease (n=6), and withdrawal of consent (n=4). Although adverse events related to the infusion system were recurrent in most patients throughout treatment and were among the reasons for discontinuation for several patients, for only 4 patients they were the sole reason for treatment discontinuation.

[1] A subset of patients included in NPP-002-02 were also included in the NPP-002-00 analysis.

DETAILED PHARMACOLOGY

Levodopa is a hydrophilic compound (log D<-2; octanol/water buffer partitioning at pH 5.5-7.4) with an expected low passive membrane diffusion. Accordingly, the high small intestinal permeability of levodopa is a consequence of an efficient transepithelial transport by the amino acid carrier for large neutral amino acids (LNAA). The dependence of gastric emptying rate on the initiation of rapid intestinal absorption is in accordance with levodopa not being absorbed from the stomach. The longer levodopa remains in the stomach or small intestine, the more extensively it is metabolised and made unavailable for absorption. It has also been shown that gastric emptying is an important factor that contributes to the large intraindividual variability seen in the plasma concentration profile of patients on oral medication, as the intraindividual variability was significantly lower after intravenous and duodenal administration in comparison with oral dosing.

The administration of levodopa in controlled release preparations does not reduce the large fluctuations in plasma concentrations to any major extent. There is no significant change in elimination half-life due to prolonged absorption, which is explained by poor colonic absorption of levodopa as the colonic human permeability is predicted to be low. This is in accordance with the distribution of the LNAA-carrier along the gastrointestinal tract and that the intestinal absorption by passive diffusion is expected to be very low due to the hydrophilic nature of the levodopa.

The principle behind constant levodopa infusion is to achieve continuous dopaminergic stimulation with an optimised dose that can be kept stable within the therapeutic window. Gastric emptying must be bypassed to achieve this. Intravenous infusions and intraduodenal infusions of levodopa or levodopa/carbidopa have been shown to reduce fluctuations in plasma levodopa concentrations and to dramatically improve mobility compared to standard oral therapy.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single-Dose Toxicology

At dosage ratios of 1:1, 1:2, 1:3, 1:4, 1:5 and 1:10 carbidopa to L-dopa, oral LD_{50} values in mice were 1930, 2280, 3270, 3090, 2940 and 3360 mg/kg, respectively. Clinical signs of toxicity were central stimulation appearing within 30 minutes of dosing and persisting 1-2 days. Deaths were mainly in the first 24 hours.

Repeat-Dose Toxicity

Rat:

Ratios of 25:250, 50:250 and 100:250 carbidopa/levodopa, with a fixed dose of 250 mg/kg/day of levodopa, given by gavage, were investigated in groups of 10 male and 10 female Sprague-Dawley rats for 26 days. The study was controlled with 10 male and 10 female rats receiving 0.5% methylcellulose. Apart from salivation, increased micturition and hyperactivity no other findings were made.

Ratios of 25:500, 50:500 and 100:500 carbidopa/levodopa, with a fixed dose of 500 mg/kg/day of levodopa, given by gavage, were investigated in groups of 10 male and 10 female Sprague-Dawley rats for 33 days. The study was controlled with 10 male and 10 female rats receiving *0.5%* methylcellulose. Mortality was recorded in all treatment groups and the high dose was killed after 19 days. Marked depression in body weight gain was recorded in the high and the intermediate groups. Meningeal haemorrhage was found in two high dose females and one intermediate group female.

Ratios of 2:1, 5:1 and 10:1 levodopa/carbidopa, with a fixed dose of 10 mg/kg/day of carbidopa, given by gavage, were investigated in groups of 70 male and 70 female Sprague-Dawley rats for 106 weeks. The study was controlled with 70 male and 70 female rats receiving 0.5% methylcellulose. Interim kills of 10 male and 10 female animals were made at 26 and 52 weeks. Ptyalism was seen in the high dose animals until week 35 and these animals were slightly sedated until week 15. There were no differences in mortality between groups. Body weight gain was decreased in the high dose animals and the intermediate dose males. Slight increases in kidney weights were found in the high dose animals at 26 weeks and high and intermediate dose animals at 52 weeks. Slight increases in liver weights were found in high and intermediate dose females at 52 weeks. No significant pathologies were found at any time points.

Monkey

Ratios of 2:1, 5:1 and 10:1 levodopa/carbidopa, with a fixed dose of 10 mg/kg/day of carbidopa, given by gavage, were investigated in groups of 6 male and 6 female rhesus monkeys for 54 weeks. The study was controlled with 6 male and 6 female monkeys receiving 0.5% methylcellulose. An interim kill of 3 males and 3 females was made at 26 weeks. Hyperactivity was noted over weeks 1-14 in the medium dose group and 1-26 weeks for the high dose group. Three deaths occurred, one low dose animal in week 6, one medium dose animal in week 15 and one control animal in week 47: these deaths were not treatment related. Hyperactivity was recorded from weeks 1-14 for the mid dose group and weeks 1-26 for the high dose group. There were no effects on body weight and haematological and biochemical parameters were

within the normal range. Dose related melanuria was found in all treated monkeys. Axonal degeneration of peripheral nerves was recorded in all treatment groups. Basophilic lamellar bodies occurred in the brain of two high dose animals.

Studies on dyskinesias in monkeys

It has been shown that squirrel monkeys treated twice daily with levodopa and carbidopa (15 mg/kg and 3.75 mg/kg, respectively, by oral gavage) for two weeks developed dyskinesias. A study in cynomolgus monkeys showed that at the dose of 80-mg/kg/day levodopa and 20-mg/kg/day carbidopa for 13 weeks developed dyskinesias, which progressively intensified over the course of the study.

Genotoxicity
In vitro and *in vivo* studies have not been conducted.

Carcinogenicity
Ratios of 2:1, 5:1 and 10:1 levodopa/carbidopa, with a fixed dose of 10 mg/kg/day of carbidopa, given by gavage, were investigated in groups of 70 male and 70 female Sprague-Dawley rats for 106 weeks. The study was controlled with 70 male and 70 female rats receiving 0.5% methylcellulose. Interim kills of 10 male and 10 female animals were made at 26 and 52 weeks. Sufficient animals survived the treatment period to allow for proper interpretation of the data. There was no alteration to the tumour profile associated with the administration of this combination product.

Reproductive and Developmental Toxicity
Fertility and early embryonic development

Groups of 12 male Sprague-Dawley rats were given ratios of 2:1, 5:1 and 10:1 levodopa/carbidopa, with a fixed dose of 10 mg/kg/day of carbidopa, by oral gavage, for 70 days and each male mated to three untreated females. The control group was of 20 male animals. The females were killed on day 14 gestation. No effects were seen on the number of pregnancies, implantations, resorptions or foetuses per female when compared to the controls.

Groups of 24 female Sprague-Dawley rats were given ratios of 2:1, 5:1 and 10:1 levodopa/carbidopa, with a fixed dose of 10 mg/kg/day of carbidopa, by oral gavage, for 14 days and mated to untreated males. The control group was of 42 female animals. Half the animals were killed on day 14 and the other half allowed to litter. No effects were seen on the number of pregnancies, implantations, resorptions or foetuses per female when compared to the respective controls.

Embryofetal development

Ratios of 250:25, 250:50, 250:125 and 500:100 mg/kg/day levodopa/carbidopa were administered, by oral gavage, to groups of 23 pregnant CF1 mice from day 6-15 of gestation. The study was controlled with a group of 46 pregnant animals. In animals receiving the 250:125 and 500:100 mg/kg/day of levodopa/carbidopa significant decreases of foetal weights were found and the number of stunted foetuses was higher than the controls. There was no increase in foetal mortality and malformations in comparison to the controls.

Ratios of 2.5:25, 12.5:125 and 25:250 mg/kg/day levodopa/carbidopa were administered by oral gavage to groups of 32 pregnant CF1 mice from day 6-15 of gestation. The study was controlled with a group of 32 pregnant animals. On day 19, 18 females from each group were killed and the foetuses examined. One third of the foetuses were examined for visceral malformations and two thirds for skeletal abnormalities. 14 females from each group were permitted to litter normally and the pups observed for 4 weeks. Of the 32 females on each dose 18, 19, 21 and 13 were pregnant from the control, low, intermediate and high dose, respectively. There were no effects on maternal or pup weight gains. No abnormalities above control values were found. At week 4 the number alive was marginally lower in animals dosed at the high combination dosage.

Ratios of 125:62.5, 187:37.5 and 250:25 mg/kg/day levodopa/carbidopa were administered by oral gavage to groups of 10 pregnant New Zealand White rabbits from day 7-15. The study was controlled with a group of 25 pregnant rabbits. There was decreased weight of the live foetuses in all test groups. The number of resorptions was increased. Visceral abnormalities of the lung, heart and greater vessels, together with skeletal deformities were found at all dose levels. These effects are attributable to levodopa.

The ratio of 125:12.5 mg/kg/day of levodopa/carbidopa was administered by gavage to 21 pregnant Sprague-Dawley rats from day 7-15 of gestation. The study was controlled with a group of 31 pregnant animals. 11 females from each group were killed at day 21 and the other 10 animals allowed to litter. No differences were observed in numbers of resorptions, implants, pregnant females, live pups per litter or foetal abnormalities. In females allowed to litter, the average number of live pups were 14.7 for controls and 10.7 for the treated group.

Prenatal and postnatal development, including maternal function

Ratios of 2:1, 5:1 and 10:1 of levodopa/carbidopa, with a fixed dose of 10-mg/kg/day carbidopa, were given by gavage to groups of 20 pregnant Sprague-Dawley rats from day 15-21 of gestation. The study was controlled with a group of 35 pregnant animals. There was an indication that the length of gestation was prolonged. No effects were recorded on the number of pups per litter or weaning or weight of pups. Three high dose level pups were found with abnormalities.

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PART III: CONSUMER INFORMATION

PrDUODOPA™
(levodopa/carbidopa intestinal gel)

DUODOPA, for use in the treatment of advanced levodopa-responsive Parkinson's disease when satisfactory control of severe, disabling motor symptoms cannot be achieved with available combinations of Parkinson medications has been approved with conditions, pending the results of studies to verify its clinical benefit. For more information, contact your healthcare provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Information in this leaflet is intended for patients and/or caregivers. "You" refers to the patient or someone in your care.

This leaflet is part III of a three-part "Product Monograph" published when DUODOPA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DUODOPA. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medication, even if you have taken this drug before. Keep this leaflet with your medication in case you need to refer to it again.

ABOUT THIS MEDICATION

What the medication is used for:

DUODOPA contains a combination of levodopa and carbidopa, which is used to treat the signs and symptoms of Parkinson's disease.

DUODOPA is a levodopa and carbidopa combination in the form of a gel that is administered directly into the small intestine. This type of treatment is mainly for use in patients with advanced Parkinson's disease who do not have satisfactory control of severe, disabling motor symptoms with available combinations of medications for Parkinson's disease.

What DUODOPA does:

Levodopa is transformed in the body to dopamine, a substance that is naturally present in the brain and spinal cord. Dopamine helps nerve cells in the brain that control movement to function properly. Too little dopamine can cause symptoms like those seen in Parkinson's disease, e.g. tremor, rigidity/muscular stiffness, slow movements, difficulty keeping one's balance. Treatment with levodopa increases the amount of dopamine in the brain and reduces these symptoms.

Carbidopa is used in combination with levodopa to ensure that enough levodopa gets to the brain where it is needed. This improves the effect and reduces the undesirable effects of levodopa, such as upset stomach.

DUODOPA is a gel that is administered throughout the day with a pump via a tube, directly into the duodenum (the beginning portion of the small intestine). This means that the two active ingredients are received continuously over the day. Consequently, the amount of drug in the blood becomes more constant and the risk of symptoms such as movement disorders is reduced.

When DUODOPA should not be used:

- **if you have a history of complications or problems with your stomach and/or intestines (such as swelling or obstruction) or with your pancreas that prevents placement of a PEG tube.**
- if you are hypersensitive (allergic) to levodopa, carbidopa or any of the other ingredients of DUODOPA.
- if you have narrow-angle glaucoma
- if you have kidney disease.
- if you have severe heart disease
- if you have severe cardiac arrhythmia (irregular heartbeat)
- if you have had an acute stroke
- if you have been treated during the last two weeks with a MAO-inhibitor, such as for depression or Parkinson's disease
- if you have a tumour of the adrenal gland
- if you have hormonal problems (over-production of the adrenal or thyroid hormones)

- if you have been told you should not take sympathomimetic drugs such as isoproterenol, amphetamines, epinephrine or cough and cold medications containing drugs related to epinephrine

Be sure to tell your doctor if you have had any of the above.

What the medicinal ingredient is:
The active substances are levodopa and carbidopa.

What the important nonmedicinal ingredients are:
Other ingredients are carmellose sodium and purified water.

What dosage forms DUODOPA comes in:
Intestinal gel (1 mL DUODOPA contains 20 mg levodopa and 5 mg carbidopa, monohydrate).

100 mL of DUODOPA is contained in a PVC bag, which is kept inside a hard plastic casette while connected to the portable pump.

WARNINGS AND PRECAUTIONS

Some people feel sleepy, drowsy, or, rarely, may suddenly fall asleep without warning (i.e. without feeling sleepy or drowsy) when taking levodopa. During treatment with DUODOPA take special care when you drive or operate a machine. If you experience excessive drowsiness or a sudden sleep onset episode, refrain from driving and operating machines, and contact your physician.

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. Therefore, your doctor should perform periodic skin examinations.

Your doctor will need to carefully examine your overall condition to determine if DUODOPA treatment will be suitable for you.

Before beginning treatment with DUODOPA it is important that you tell your doctor about any other medical problems that you have or have had including:

- irregular heart rhythm or history of heart attack
- severe lung problems, asthmatic bronchitis
- glaucoma
- hormonal disturbances
- severe liver or kidney disease
- depression or any mental disorder
- gastric ulcer or previous surgery in the upper part of your abdomen
- a history of convulsions
- skin cancer or suspicious skin cancer
- allergies to any other medicines, foods, dyes or preservatives

It is also important to tell your doctor before beginning treatment:

- if you drive or operate machinery
- if you are going to have an operation that requires general anesthesia

Use in Children
DUODOPA has not been studied in and should not be given to children or young people under 18 years (due to lack of clinical experience).

Pregnancy
If you are pregnant or think you may be pregnant, do not use DUODOPA before consulting your doctor.

Breast-feeding
You should not breast-feed while under treatment with DUODOPA.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including drugs that you can buy without a prescription.

It is important to tell your doctor if you are already taking or have recently taken:

- drugs used for the treatment of depression, such as MAO inhibitors or tricyclic antidepressants
- drugs used for the treatment of schizophrenia, tuberculosis, high blood pressure, muscle twitches or epileptic convulsions
- sympathomimetic drugs, such as isoproterenol, amphetamines, or cough and cold medications containing epinephrine
- iron tablets or multivitamin tablets containing iron

You should also tell your doctor about all medications that you are taking for Parkinson's disease.

Protein rich diets (for example, a lot of meat, poultry or fish) may reduce the beneficial effects of levodopa.

PROPER USE OF THIS MEDICATION

DUODOPA should only be prescribed by a doctor who is experienced in treating patients with Parkinson's disease and who has completed the DUODOPA Education Program. The DUODOPA Education Program provides training to doctors and nurses for the safe and effective use of this treatment. Your doctor or trained health care professional will guide you on the proper use and administration of DUODOPA.
Only the CADD-Legacy DUODOPA pump should be used for administration of DUODOPA. The FLOCARE PEG Tube is one of the PEG tubes that may be used with the CADD-Legacy DUODOPA pump. Please see information below for care and maintenance of these components.

Before you have surgery to insert a tube directly into the upper small intestine, your doctor will usually first insert a temporary tube through the nose into the small intestine for at least a few days, to see if you respond well to DUODOPA treatment and to adjust the dose.

Usual dose:
Always use DUODOPA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure. The dose of DUODOPA is different for each patient and may need regular small adjustments, to reach the best dose for your symptoms. Your prescription is programmed into your pump by your doctor/nurse and should only be adjusted by your doctor/nurse if your medication needs change.

Usually, a larger morning dose is administered with the pump (bolus dose) to quickly reach the correct blood level of levodopa. After that a lower maintenance dose is given continuously throughout the day, until bedtime. If needed, extra doses may be given, following your doctor's recommendations.

Use of the CADD-Legacy DUODOPA Pump
Before starting medication delivery, carefully inspect the tubing and connections for kinks or other blockages. An undetected kink or blockage may result in too little or no medication delivery and/or nuisance alarms from the pump.

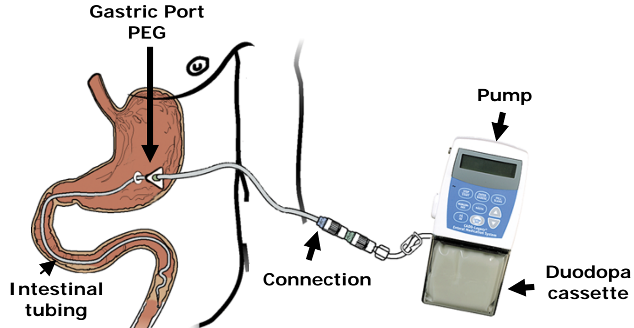
To attach the cassette to the pump:

1. Clamp the tubing.
2. Insert the cassette hooks into the hinge pins on the pump.
3. Place the pump upright on a firm, flat surface. Press down so the cassette fits tightly against the pump.
4. Insert a coin into the latch, push in, and turn counterclockwise until the line on the latch lines up with the arrow on the side of the pump and you feel the latch click into place.
5. Gently twist, push and pull on the cassette to make sure it is firmly attached. If the cassette is not secure, repeat the procedure.

An improperly attached cassette could result in an error in your dosing.

For more details on how to handle the pump, an **Instruction Manual** is provided with the pump.

The following diagram shows how all the components of the DUODOPA system should look when in use.



Abrupt or unintentional stopping of treatment:
Do not change the dosage or stop DUODOPA treatment without talking to your doctor.

- Abrupt interruption of treatment may result in complications.
- If your symptoms suddenly or slowly become worse it is possible that the tube in the small intestine is blocked, disconnected or has moved. If this happens call your doctor immediately.

Intentional stopping of treatment:
If you wish to stop treatment with DUODOPA talk to your doctor. Your doctor will remove the tube to allow the wound to heal. Treatment will continue with levodopa tablets taken by mouth.

Overdose:
If you have taken too large a dose of the drug always contact your doctor or trained health practitioner, or go to your nearest hospital.

Care of the CADD-Legacy Duodopa pump
To clean the pump and accessories, dampen a soft, lint free cloth with soapy water and wipe the exterior surface of the pump. Do not immerse the pump in water or cleaning fluid. Do not use acetone, solvents or abrasive cleaners. Wipe the surface dry with another soft, lint-free cloth. Allow the pump to dry completely before use.

Maintenance and Care of the Intestinal Tubing:
The external PEG tubing and connectors should be cleaned regularly with warm, soapy water.

The intestinal tube should be flushed with tap water every night to prevent blockages. **During the initial test phase DO NOT flush the naso-intestinal tube as this can result in too much medication entering your body at one time.**
The extension tube should be removed, capped and placed in the refrigerator each night. The extension tube should not be flushed.

When internal and external tubing has been in place for more than a year, your doctor should assess its functioning regularly.

Maintenance and Care of the Surgical wound:
The dressing on your surgical wound should be changed daily for the first three weeks.

The tube opening should be cleaned with soap and water during showers and baths. Make sure that the skin is properly dried afterwards.

If the tube wound becomes red and swollen, or infected, contact your doctor.

Do not administer any substances other than DUODOPA into your PEG tube without consulting your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DUODOPA can cause side effects. You may not experience any of them. If you experience any of these side effects, contact your doctor as soon as you can. Many of the side effects can be relieved by adjusting the dose.

Side effects that can be caused by levodopa
Common:
- loss of appetite, upset stomach, vomiting, dry mouth, bitter taste
- hallucinations, confusion, nightmares, sleepiness, fatigue, sleeplessness, feeling sad, exaggerated feeling of happiness, delusions, loss of concentration and memory, agitation
- involuntary movements (dyskinesias), muscle cramps,
- dizziness
- heart palpitations, irregular heartbeat, fainting

Uncommon:
- loss of weight, increased weight
- walking disturbances, tremor of the hands
- high blood pressure
- hoarseness, chest pain
- constipation, diarrhea, increased salivation, difficulty swallowing, flatulence
- swelling (edema)
- muscle spasms
- dark-colored urine
- weakness, feeling of discomfort (malaise)

Rare:
- fear, reduced thinking, disorientation, increased sexual desire, numbness
- drowsiness and sleepiness (somnolence),
- burning/prickling sensation of skin, falling, walking defects, spasm of jaw muscles, headache and convulsions.
- blurred vision, involuntary winking (contraction of eyelid muscle), double vision
- inflammation of veins (phlebitis)
- shortness of breath, abnormal breathing pattern
- indigestion, abdominal pain, dark-colored saliva, teeth grinding, hiccups, burning sensation of the tongue, duodenal (beginning portion of the small intestine) ulceration
- itching, rash, flushing, hair loss, increased sweating, dark colored sweating
- difficulty urinating, inability to control urinating, prolonged and painful erection

Very rare:
- falling asleep without warning
- changes in behavior, such as compulsive gambling

Side effects caused from the intestinal tube
The following common complications have been reported for the tube system:
- dislocation of the intestinal tube to the stomach, knot in tube, blockage of tube (which leads to decrease in treatment response)
- local infection around the tube through the abdominal wall
- secretion/leakage or swollen flesh around tube through abdominal wall
- stomach pain

If any problem occurs with the pump or the tube system please contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk to your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Allergic reaction such as: redness, itching or swelling of your skin, hives; swelling around eyes or lips, swelling of hands, feet or throat; any trouble with breathing, not present before using this medicine		✓	
Common	Irregular heartbeat, feeling dizzy or faint when standing up, fainting		✓	
Common	Changes in mental condition such as hallucinations, depression	✓		
Rare	Inability to urinate		✓	
Very rare	Falling asleep without warning		✓	

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking DUODOPA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 2ºC-8ºC (in a refrigerator).

Close the carton carefully. DUODOPA is sensitive to light.

The cassettes with intestinal gel should be kept out of reach and sight of children.

The drug cassettes are for one time use only and should not be used for longer than one day (up to 16 hours) even if some intestinal gel remains. Use before the expiry date printed on the carton. Used cassettes should not be reused but returned to a designated pharmacy.

By the end of the storage time the gel might become slightly yellow. This does not affect the amount of the drug or the treatment.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.hc-sc.gc.ca (Drug Product Database) or by contacting the sponsor, Abbott Laboratories, Limited, at: 1-800-699-9948

This leaflet was prepared by Abbott Laboratories, Limited

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