

## Prescribing Information

### 1. NAME OF THE MEDICINAL PRODUCT

Duodopa®

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

### 3. PHARMACEUTICAL FORM

Intestinal gel

White to slightly yellow gel.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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

A positive test of the clinical response to Duodopa administered via a temporary nasoduodenal tube is required before a permanent tube is inserted.

#### 4.2 Posology and method of administration

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

A temporary nasoduodenal tube is recommended to find out if the patient responds favourably to this method of treatment and to adjust the dose before treatment with a permanent tube is started.

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

Duodopa should be given initially as monotherapy. If required other medicinal products for Parkinson's disease can be taken concurrently. For administration of Duodopa only the CADD-legacy Duodopa pump (CE 0473) should be used. *A manual with instructions for using the portable pump is delivered together with the pump.*

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

**Dosage:**

The total dose/day of Duodopa is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses.

Morning dose: The morning bolus dose is administered by the pump to rapidly achieve the therapeutic dose level (within 10-30 minutes). The dose should be based on the patient's previous morning intake of levodopa + the volume to fill the tubing. The total morning dose is usually 5-10 ml, corresponding to 100-200 mg levodopa. The total morning dose should not exceed 15 ml (300 mg levodopa).

Continuous maintenance dose: The maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The dose should be calculated according to the patient's previous daily intake of levodopa. When supplementary medicines are discontinued the Duodopa dose should be adjusted. The continuous maintenance dose is adjusted individually. It should be kept within a range of 1-10 ml/hour (20-200 mg levodopa/hour) and is usually 2-6 ml/hour (40-120 mg levodopa/hour). The maximum recommended daily dose is 200 ml (see section 4.4). In exceptional cases a higher dose may be needed.

*Example:*

Daily intake of levodopa as Duodopa: 1640 mg/day

Morning bolus dose: 140 mg = 7 ml (excluding the volume to fill the intestinal tube)

Continuous maintenance dose: 1500 mg/day

1500 mg/day: 20 mg/ml = 75 ml Duodopa per day

The intake is calculated over 16 hours: 75 ml/16 hours = 4.7 ml/hour.

Extra bolus doses: To be given as required if the patient becomes hypokinetic during the day.

The extra dose should be adjusted individually, normally 0.5-2.0 ml. In rare cases a higher dose may be needed. If the need for extra bolus doses exceeds 5 per day the maintenance dose should be increased.

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

If medically justified Duodopa may be administered during the night.

*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.

Paediatric population

There is no relevant indication for use of Duodopa in children and adolescents.

Geriatric Population

There is considerable experience in the use of levodopa/carbidopa in elderly patients. The dosage recommendations set out above reflect the clinical data derived from this experience.

Renal/hepatic impairment

No dose adjustment is necessary.

Interruption of therapy

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

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

When a cassette is about to be used, it should be attached to the portable pump and the system connected to the nasoduodenal tube or the transabdominal port/duodenal tube for administration, according to the instructions given. The drug cassettes are for single use only and should not be used for longer than one day (up to 16 hours) even if some medicinal product remains. Do not reuse an opened cassette.

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

#### **4.3 Contraindications**

Duodopa is contraindicated in patients with:

- hypersensitivity to levodopa, carbidopa or any of the excipients
- narrow-angle glaucoma
- severe liver and renal insufficiency
- severe heart failure
- severe cardiac arrhythmia
- acute stroke
- Non-selective MAO inhibitors and selective MAO type A inhibitors must not be given concomitantly, and should be withdrawn at least two weeks before initiation of Duodopa, see section 4.5.
- Conditions in which adrenergics are contraindicated, e. g. pheochromocytoma, hyperthyroidism and Cushing's syndrome.

#### **4.4 Special warnings and precautions for use**

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

- Duodopa is not recommended for the treatment of drug-induced extrapyramidal reactions.
- Duodopa therapy should be administered with caution to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions.
- In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments.
- All patients treated with Duodopa should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious mental changes. Patients with past or current psychosis should be treated with caution.
- Concomitant administration of antipsychotics with dopamine receptor blocking properties, particularly D2 receptor antagonists should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms, see section 4.5.
- Patients with chronic wide-angle glaucoma may be treated with Duodopa with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure.
- Duodopa may induce orthostatic hypotension. Therefore Duodopa should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension, see section 4.5.
- Levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should therefore be exercised when driving and operating machines.
- A symptom complex resembling Neuroleptic Malignant Syndrome (NMS), including muscular rigidity, increased body temperature, mental changes (e.g. agitation, confusion, coma) and increased serum creatine phosphokinase, has been reported when anti-Parkinsonian medicinal products were withdrawn abruptly. Rhabdomyolysis secondary to Neuroleptic Malignant Syndrome or severe dyskinesias have been observed rarely in patients with Parkinson's disease. Therefore, patients should be carefully observed when the dose of levodopa/carbidopa combinations are abruptly reduced or discontinued, especially if the patient is receiving anti-psychotics. Neither NMS nor rhabdomyolysis has been reported in association with Duodopa.
- Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control

disorders including pathologic gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Duodopa. Review of treatment is recommended if such symptoms develop.

- If general anaesthesia is required, treatment with Duodopa may be continued for as long as the patient is permitted to take fluids and medicinal products by mouth. If therapy has to be stopped temporarily, Duodopa at the same dose as before may be restarted as soon as oral intake of fluid is allowed.
- The dose of Duodopa may need to be adjusted downwards in order to avoid levodopa induced dyskinesias.
- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Duodopa.
- Duodopa contains hydrazine, a degradation product of carbidopa that can be genotoxic and possibly carcinogenic. The average recommended daily dose of Duodopa is 100 ml, containing 2 g levodopa and 0.5 g carbidopa. The maximum recommended daily dose is 200 ml. This includes hydrazine at up to an average exposure of 4 mg/day, with a maximum of 8 mg/day. The clinical significance of this hydrazine exposure is not known.
- Previous surgery in the upper part of the abdomen may lead to difficulty in performing gastrostomy or jejunostomy
- Isolated reports have been received describing gastrostomy tube blockage and/or intestinal obstruction with bezoar formation, necessitating replacement of tubing and in rare cases surgery. Early symptoms include aggravation of Parkinson's symptoms, reduced efficacy, abdominal pain, nausea, and vomiting. In some cases, gastric and intestinal ulcerations have been found. Bezoars are retained concretions of undigested food material in the intestinal tract. Most bezoars reside in the stomach but bezoars may be encountered elsewhere in the intestinal tract.
- Reduced ability to handle the system (pump, tube connections) can lead to complications. In such patients a caregiver (e.g. nurse, assistant nurse, or close relative) should assist the patient.
- A sudden or gradual worsening of bradykinesia may indicate an obstruction in the device for whatever reason and needs to be explored.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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

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

##### Antihypertensives

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

##### Antidepressants

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic antidepressants and carbidopa/levodopa preparations, see section 4.3.

##### Anticholinergics

Anticholinergics may act synergistically with levodopa to decrease tremor. However, combined use may exacerbate abnormal involuntary movements. Anticholinergics may decrease the effects of levodopa by delaying its absorption. An adjustment of the dose of Duodopa may be needed.

##### COMT inhibitors (tolcapone, entacapone)

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

##### Other medicinal products

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

Duodopa can be taken concomitantly with the recommended dose of an MAO inhibitor, which is selective for MAO type B (for instance selegiline-HC1).

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

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

Sympathomimetics may increase cardiovascular adverse events related to levodopa.

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

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

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

#### 4.6 Pregnancy and lactation

##### Pregnancy

There are no adequate data from the use of levodopa/carbidopa in pregnant women. Data from animal studies have shown reproduction toxicity, see section 5.3. The potential risk for humans is unknown. Duodopa should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus.

##### Lactation

Levodopa is excreted in the breast milk. There is evidence that lactation is suppressed during treatment with levodopa. It is unknown whether carbidopa is excreted in human breast milk. Animal studies have shown excretion of carbidopa in breast milk. The safety of levodopa and carbidopa in the infant is not known. Duodopa should not be used during breast-feeding.

#### 4.7 Effects on ability to drive and use machines

Levodopa and carbidopa may cause dizziness and orthostatic hypotension. Therefore, caution should be exercised when driving or using machines. Patients being treated with Duodopa and presenting with somnolence and/or sudden sleep episodes must be advised to refrain from driving or engaging in activities where impaired alertness may put them, or others, at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved, see also section 4.4.

#### 4.8 Undesirable effects

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

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
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<b>Blood and lymphatic system disorders</b>			Leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia	Agranulocytosis
<b>Metabolism and nutrition disorders</b>	Anorexia	Loss of weight, increased weight		
<b>Psychiatric disorders</b>	Hallucinations, confusion, nightmares, sleepiness, fatigue, sleeplessness, depression with very rare suicide attempts, euphoria, dementia, psychotic episodes, feeling of stimulation		Agitation, fear, reduced thinking capacity, disorientation, increased libido, numbness	
<b>Nervous system disorders</b>	Dyskinesias, choreatic movements and dystonia, "ON-OFF" episodes, dizziness, bradykinesia ("ON-OFF" episodes) <sup>1</sup> , somnolence <sup>2</sup>	Ataxia, increased tremor of the hands	Neuroleptic malignant syndrome, paraesthesias, falling, walking defects, trismus, headache, convulsions	
<b>Eye disorders</b>			Blurred vision, blepharospasm (see section 4.9), activation of a latent Horner's syndrome, double vision, dilated pupils, oculozytic crises	
<b>Cardiac disorders</b>	Palpitations, irregular heartbeat			
<b>Vascular disorders</b>	Orthostatic hypotension, inclination to faint, syncope	Hypertension	Phlebitis	
<b>Respiratory, thoracic and mediastinal</b>		Hoarseness, chest pain	Dyspnoea, abnormal breathing pattern	

<sup>1</sup> 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 adaption of dose schedule and dose intervals may be required.

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

<b>disorders</b>				
<b>Gastrointestinal disorders</b>	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	
<b>Skin and subcutaneous tissue disorders</b>		Oedema	Angiooedema, urticaria, pruritus, facial redness, hair loss, exanthema, increased perspiration, dark perspiration fluid, malignant melanoma, Schönlein-Henoch purpura	
<b>Musculoskeletal, connective tissue and bone disorders</b>		Muscle spasms		
<b>Renal and urinary disorders</b>		Dark urine	Urinary retention, urinary incontinence, priapism	
<b>General disorders and administration site reactions</b>		Weakness, malaise		

Other adverse reactions have been reported in association with levodopa/ carbidopa combinations including Duodopa:

*Impulse control disorders:* Pathological gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Duodopa (see section 4.4. 'Special warnings and precautions for use').

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

*The device:* Complications with the device are very common ( $\geq 1/10$ ), e.g. connector leakage, dislocation of the intestinal tube. Dislocation of the intestinal tube backwards into the stomach leads to reappearance of motor fluctuations (due to erratic gastric emptying of Duodopa into

the small intestines). In general, relocation of the tube can be done using a guide-wire to steer the tube into the duodenum under fluoroscopy. 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, knotting, or a tube displacement may need readjustment of the tubing. Should complete failure of the intestinal tube or pump occur the patient must be treated with oral levodopa/ carbidopa until the problem is solved. The stoma usually heals without complications. However, abdominal pain, infection and leakage of gastric fluid may occur shortly after surgery; it is rarely a problem long-term. Reported complications include perforation of adjacent anatomical structures especially during PEG placement and bleeding, wound infection (the most common complication) and peritonitis. Local infections around the stoma are treated conservatively with a disinfectant. Treatment with antibiotics is rarely needed.

**There have been isolated reports of bezoar formation (see 4.4).**

#### **4.9 Overdose**

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

The treatment of an acute overdose of Duodopa is in general the same as that of an acute overdose of levodopa: However, pyridoxine has no effect on the reversal of the action of Duodopa. Electrocardiographic monitoring should be used and the patient observed carefully for the development of cardiac arrhythmias; if necessary an appropriate antiarrhythmic therapy should be given. The possibility that the patient took other medicinal products together with Duodopa should be taken into consideration. To date experiences with dialysis have not been reported, therefore its value in the treatment of overdose is unknown.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

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

Intestinal therapy with Duodopa reduces the motor fluctuations and increases the "ON"-time for patients with advanced Parkinson's disease who have received tablet treatment with levodopa/decarboxylase inhibitor for many years. The motor fluctuations and hyper-/dyskinesias are reduced due to the fact that the plasma concentrations of levodopa are being kept at a steady level within the individual therapeutic window. Therapeutic effects on motor fluctuations and hyper-/dyskinesias are often achieved during the first treatment day.

### **5.2 Pharmacokinetic properties**

#### Absorption

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

#### Distribution

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

#### Metabolism and elimination

The elimination half-life for levodopa is approximately 1-2 hours. Levodopa is eliminated completely through metabolism and the metabolites formed are excreted mainly in the urine. Four metabolic pathways are known, decarboxylation being predominant for levodopa administered without any enzyme inhibitor. When levodopa is co-administered with carbidopa the decarboxylase enzyme is inhibited so that metabolism via catechol-O-methyl-transferase (COMT) becomes the dominant metabolic pathway.

#### Pharmacokinetic-pharmacodynamic relationship

The reduced fluctuations in the plasma concentration of levodopa reduce fluctuations in the treatment response. The levodopa dose needed varies considerably in 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. On the contrary, many patients, after a period of satisfactory treatment with Duodopa, may find that a lower dose of levodopa will provide a satisfactory clinical response.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In reproductive toxicity studies both levodopa and the combination of carbidopa/levodopa have caused visceral and skeletal malformations in rabbits.

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Carmellose sodium  
Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

Unopened: 15 weeks.

Once opened: Use immediately. Discard any unused portion.

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

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C-8°C).

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

### **6.5 Nature and contents of container**

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

### **6.6 Special precautions for disposal and other handling**

Cassettes are for single use only.

Do not re-use an opened cassette.

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

**7. Manufacturer: Abbott Products GmbH**, Hans-Bockler-Allee 20, Hannover, Germany

**8. Marketing authorization holder:** Abbott Medical Laboratories Ltd., P.O. Box 58099, Tel Aviv 61580

**9. Marketing authorization number**  
**143 – 32- 32029 – 00**

*The format of this leaflet was determined by the Ministry of Health and its content was checked and approved*