ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 140 mg/35 mg modified-release hard capsules
Hopledo 210 mg/52.5 mg modified-release hard capsules
Hopledo 280 mg/70 mg modified-release hard capsules
Hopledo 350 mg/87.5 mg modified-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hopledo 140 mg/35 mg modified-release hard capsules

Each modified-release hard capsule contains 140 mg levodopa and carbidopa monohydrate equivalent to 35 mg carbidopa

Excipient with known effect
Each modified-release hard capsule contains 0.0024 mg of propylene glycol

Hopledo 210 mg/52.5 mg modified-release hard capsules

Each modified-release hard capsule contains 210 mg levodopa and carbidopa monohydrate equivalent to 52.5 mg carbidopa

Excipient with known effect
Each modified-release hard capsule contains 0.0027 mg of propylene glycol

Hopledo 280 mg/70 mg modified-release hard capsules

Each modified-release hard capsule contains 280 mg levodopa and carbidopa monohydrate equivalent to 70 mg carbidopa

Excipient with known effect
Each modified-release hard capsule contains 0.0036 mg of propylene glycol

Hopledo 350 mg/87.5 mg modified-release hard capsules

Each modified-release hard capsule contains 350 mg levodopa and carbidopa monohydrate equivalent to 87.5 mg carbidopa

Excipient with known effect
Each modified-release hard capsule contains 0.0045 mg of propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsule, hard.

Hopledo 140 mg levodopa and 35 mg carbidopa modified-release hard capsules

Hard capsules with white opaque body and yellow opaque cap. Body imprinted with “140” in black ink and cap imprinted with “IPX203” in white ink. Filled capsules are 18 mm x 6 mm in size and contain white to off-white granules and beads.

Hopledo 210 mg levodopa and 52.5 mg carbidopa modified-release hard capsules

Hard capsules with white opaque body and green opaque cap. Body imprinted with “210” in black ink and cap imprinted with “IPX203” in white ink. Filled capsules are 20 mm x 7 mm in size and contain white to off-white granules and beads.

Hopledo 280 mg levodopa and 70 mg carbidopa modified-release hard capsules

Hard capsules with white opaque body and purple opaque cap. Body imprinted with “280” in black ink and cap imprinted with “IPX203” in white ink. Filled capsules are 23 mm x 8 mm in size and contain white to off-white granules and beads.

Hopledo 350 mg levodopa and 87.5 mg carbidopa modified-release hard capsules

Hard capsules with white opaque body and medium orange opaque cap. Body imprinted with “350” in black ink and cap imprinted with “IPX203” in white ink. Filled capsules are 23 mm x 9 mm in size and contain white to off-white granules and beads.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hopledo is indicated for the treatment of adult patients with Parkinson’s disease and moderate to severe motor fluctuations who have not been sufficiently stabilised with oral levodopa/dopa decarboxylase (DDC) inhibitor-based treatment regimens.

4.2 Posology and method of administration

Posology

Each capsule strength may be used alone, or in combination with other capsule strengths as required.

Use of this medicinal product with other levodopa containing medicinal products has not been studied.

Immediate-release levodopa and controlled-release levodopa, or any other combination of Parkinson’s disease treatment that contains immediate-release levodopa should not be used together with Hopledo.

Based on medical judgment, rescue levodopa medicinal product may be administered only if clinically necessary, as determined by the treating physician.

Dose recommendations should be followed at initiation of treatment and adapted according to clinical response.

Converting patients from other levodopa/dopa-decarboxylase (DDC) inhibitor immediate-release medicinal products to Hopledo
The doses of immediate-release levodopa/carbidopa products are not interchangeable on a 1:1 basis with the doses of Hopledo.

To convert patients from immediate-release levodopa/carbidopa to Hopledo, the patient’s most frequent single dose of immediate-release levodopa/DDC inhibitor should be determined, and the dosing conversion guidelines provided in Table 1 should be followed for initial dosing.

Table 1: Guidelines for initial conversion from immediate-release (IR) levodopa/DDC inhibitor medicinal to Hopledo in Parkinson’s disease patients.

Total daily IR levodopa dose	Most frequent* IR levodopa single dose (in mg)	Recommended initial dose of Hopledo (levodopa in mg)
<500 mg	100	280 two times daily

	150	420 two times daily
	200	560 two times daily
⩾500 mg	100	280 three times daily
	150	420 three times daily
	200**	560 three times daily
	>200**	700 three times daily

(*) For patients where two or more immediate-release levodopa doses correspond to the most frequent immediate-release levodopa doses, the suggested Hopledo conversion should be dosed based on the higher of the immediate-release levodopa/carbidopa doses.

(**) For patients whose most frequent immediate-release levodopa dose is 200 mg or higher, clinicians may consider initiating Hopledo using the next lower available capsule strength (70 mg less levodopa per dose) than that derived from the strict 2.8-fold conversion.

After the initial conversion, patient follow-up after 1 to 3 days is recommended, with subsequent adjustment of the dose or dosing frequency based on the individual patient's response to achieve the optimal balance of efficacy and tolerability. Clinical experience with total daily Hopledo doses above 2100 mg is limited; therefore, care should be taken when considering further dose increases and, in any case, the maximum daily doses of 2380 mg/595 mg should not be exceeded. The total daily dose can be divided up to four doses per day.

Converting patients from immediate-release levodopa / carbidopa plus Catechol-O-methyltransferase (COMT) inhibitor medicinal products to Hopledo

For patients currently treated with levodopa /carbidopa plus a catechol-O-methyltransferase (COMT) inhibitor (e.g., entacapone or opicapone), the initial total daily dose of levodopa in Hopledo may need to be increased if the COMT inhibitor is discontinued.

Maintenance

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended. Therapy should be individualised and adjusted for each patient according to the desired therapeutic response.

Addition of other medicinal products for the treatment of Parkinson's disease

Hopledo may be used together with other medicinal products for the treatment of Parkinson's disease. However, dose adjustments may be required (see section 4.5).

Interruption of therapy

Sporadic cases of withdrawal-induced hyperpyrexia and confusion presenting with a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in association with dose reductions and withdrawal of levodopa/carbidopa containing medicinal products. Patients should be observed carefully if abrupt reduction or discontinuation of the modified-release levodopa/carbidopa medicinal product is required, especially if the patient is receiving antipsychotics. The daily dose of Hopledo should be tapered at the time of treatment discontinuation (see section 4.4).

If general anaesthesia is required, the modified-release levodopa/carbidopa capsule medicinal product may be continued as long as the patient is permitted to take oral medicinal products. If therapy is interrupted temporarily (e.g. for the duration of procedure), the usual dose should be administered as soon as the patient is able to take oral medicinal products.

Special populations

Elderly

No dose adjustment of Hopledo is required for elderly. In patients aged 75 years and older experience with Hopledo is limited and these patients should be converted cautiously from immediate-release levodopa/DDCI. Close clinical monitoring is recommended during the conversion period and subsequent dose optimisation, in line with standard clinical practice for older patients during dopaminergic therapy adjustments (see Section 4.4).

Renal and Hepatic impairment
Impact of renal function on levodopa/carbidopa clearance is limited. There are no studies on the pharmacokinetics of Hopledo in patients with hepatic or renal impairment. Dosing with Hopledo is individualised by titration to optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures); therefore, potential effects of hepatic or renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration (see sections 4.4 and 5.2). Nevertheless, dose adjustment should be conducted with caution in patient with moderate to severe renal impairment and severe hepatic impairment, with appropriate clinical monitoring.

Paediatric population
The safety and efficacy of Hopledo in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Hopledo is for oral administration.

Hopledo should be swallowed whole with or without food. However, the medicinal product should not be heated or added to hot food, because heating may change the properties of Hopledo. Following administration with high-fat, high-calorie meal, absorption of levodopa may be slower, as reflected by a delayed median Tmax compared with the fasted state, while overall systemic exposure (AUC) remains unchanged. For patients in whom a rapid onset of effect is considered important, such as at the first dose of the day, administration on an empty stomach may be considered.

For patients who have difficulty swallowing, the entire content of Hopledo may be sprinkled on 1 to 2 tablespoons of applesauce and should be taken immediately. The capsule contents should not be chewed, as this may compromise the modified-release properties of the product.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Narrow-angle glaucoma.
- Phaeochromocytoma.
- Concomitant administration of non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine, tranylcypromine). These inhibitors must be discontinued at least two weeks prior to initiating therapy (see section 4.5).
- A previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

4.4 Special warnings and precautions for use

Somnolence and episodes of sudden sleep onset
Levodopa has been associated with somnolence and episodes of sudden sleep onset (see section 4.7). Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment (see section 4.7). Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dose or termination of therapy may be considered.

Withdrawal-induced hyperpyrexia and confusion
A symptom complex that resembles neuroleptic malignant syndrome (characterised by elevated temperature, muscular rigidity, altered consciousness and autonomic instability) with no other obvious aetiology, has been reported in association with rapid dose reduction, withdrawal of, or change in dopaminergic therapy (see section 4.2).

Hallucinations, psychosis, confusion

There is an increased risk of hallucinations and psychosis in patients taking levodopa.
Hallucinations may present shortly after the initiation of levodopa therapy and be responsive to levodopa dose reduction.
Hallucinations may be accompanied by confusion, insomnia, and excessive dreaming. Abnormal thinking and behaviour may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behaviour, disorientation, aggressive behaviour, agitation and delirium.

Patients with a major psychotic disorder or a history of psychotic disorder must be treated cautiously with Hopledo because of the risk of exacerbating psychosis.

In addition, medicinal products that antagonise the effects of dopamine used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of levodopa. Concomitant use of antipsychotics should be monitored carefully for worsening of Parkinson's motor symptoms especially when D2-receptor antagonists are used (see section 4.5).

Depression and suicidality
All patients should be observed carefully for the development of depression with suicidal tendencies.

Impulse control, compulsive behaviours
Patients may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, as well as the inability to control these urges while taking one or more of the medicinal products used for the treatment of Parkinson's disease that increase central dopaminergic tone.

In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medicinal product was discontinued. Because patients may not recognise these behaviours as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with Hopledo.

If a patient develops such urges reducing the dose or discontinuing Hopledo should be considered.

High levodopa doses
There is limited clinical experience with Hopledo at total daily levodopa doses above 2100 mg. Patients receiving higher doses should be monitored closely for dopaminergic adverse reactions, including orthostatic hypotension, syncope, falls and dyskinesia.

Dyskinesias
Medicinal products containing levodopa cause dyskinesias that may require treatment adjustment or dose reduction. It is recommended to monitor patients for the onset or evolution of dyskinesia and to adjust levodopa/carbidopa doses accordingly.

Orthostatic hypotension
Levodopa can cause orthostatic hypotension. Hopledo should be administered with caution with other medicinal products that may cause orthostatic hypotension, e.g. anti-hypertensive medicinal products.

Chronic wide-angle glaucoma
Patients may be treated cautiously with Hopledo provided the intraocular pressure is well-controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Melanoma
Patients and prescribing physicians are advised to monitor for melanomas frequently and on a regular basis when using levodopa/carbidopa, especially in patients with suspicious, undiagnosed skin lesions or a history of melanoma. Periodic skin examinations performed by appropriately qualified individuals (e.g., dermatologists) are recommended.

Cardiovascular ischaemic events
Levodopa should be administered with caution in patients with severe cardiovascular disease. 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 Hopledo dose adjustments.

Peptic ulcer disease
Levodopa treatment may increase the possibility of upper gastrointestinal haemorrhage in patients with a history of peptic ulcer.

Patients with comorbidities
Levodopa/carbidopa should be administered cautiously to patients with severe pulmonary disease, bronchial asthma, endocrine disease, history of convulsions, in patients with moderate to severe renal impairment and severe hepatic impairment, with appropriate clinical monitoring.

Use in elderly patients
Elderly patients aged 75 years and older may be more susceptible to dopaminergic adverse reactions. These include dyskinesia, hallucinations, confusion, somnolence, orthostatic hypotension, syncope and falls. Patients in this population should be monitored closely, especially during dose conversion and titration (see Section 4.2).

Laboratory monitoring
Decreased haemoglobin and haematocrit have been observed on long-term levodopa/carbidopa treatment. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy.

Interference with laboratory tests
Levodopa may cause a false-positive reaction for urinary ketone bodies, when a test tape is used for determination of ketonuria and this reaction will not be altered by boiling the urine specimen. False-negative test may result with the use of glucose-oxidase methods of testing for glucosuria.
Caution should be exercised when interpreting the plasma and urine measurements of catecholamines as levodopa or levodopa/carbidopa therapy may elevate their level.

Vitamin B6 deficency
Treatment with levodopa/carbidopa can lead to vitamin B6 deficiency, which may increase the risk of seizures, particularly in patients receiving higher doses, and/or those with poor nutritional status. Monitoring of pyridoxine (vitamin B6) levels and vitamin B6 supplementation should be considered in patients receiving high-dose levodopa/carbidopa and those presenting with clinical manifestations suggestive of vitamin B6 deficiency.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

This medicinal product contains propylene glycol: 0.0024 mg per capsule of 140 mg/35 mg; 0.0027 mg/ per capsule of 210 mg/52.5 mg; 0.0036 mg per capsule of 280 mg/70 mg; 0.0315 mg per capsule of 350 mg/87.5 mg.

4.5 Interaction with other medicinal products and other forms of interaction

Non-selective monoamine oxidase (MAO) inhibitors

Levodopa is contraindicated in patients treated with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine, tranylcypromine), as coadministration of levodopa with non-selective MAO inhibitors could result in hypertensive crisis. These MAO inhibitors must be discontinued at least 2 weeks prior to treatment initiation with Hopledo (see section 4.3).

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

Selective monoamine oxidase (MAO) inhibitors

The concomitant use of selective MAO-B inhibitors (such as selegiline, rasagiline and safinamide) with levodopa may be associated with severe orthostatic hypotension Patients who are taking these medicinal products should be monitored.
The dose of levodopa may need to be reduced when a MAO inhibitor selective for type B is added. Patients should be maintained on the lowest dose required to achieve symptomatic control and to minimise adverse reactions.

Dopamine D2 receptor antagonists, benzodiazepines and isoniazid

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone and metoclopramide), benzodiazepines and isoniazid may reduce the therapeutic effects of levodopa. Patients taking these medicinal products together with levodopa should be monitored carefully for loss of therapeutic response.

Tricyclic antidepressants

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and levodopa.

Antihypertensives

Symptomatic postural hypotension has occurred when combinations of levodopa and a decarboxylase inhibitor are added to the treatment of patients already receiving certain antihypertensives. Dose adjustment of the antihypertensive medicinal products may be required during the titration phase of treatment with Hopledo.

Anticholinergics

Anticholinergic medicinal products can work synergistically with levodopa, in order to improve tremor. Concurrent use can, however, cause a worsening of involuntary motor disorders. Anticholinergic medicinal products may impair the effect of levodopa, due to a delayed absorption. A dose adjustment of levodopa may be required.

Phenytoin and papaverine

There have been rare reports that the beneficial effects of levodopa in Parkinson's disease are reversed by phenytoin and papaverine. Patients taking these medicinal products with levodopa/carbidopa should be carefully monitored for loss of therapeutic response.

COMT inhibitors (tolcapone, entacapone, opicapone)

Hopledo can be used with catechol O-methyl transferase (COMT) inhibitors, such as entacapone, opicapone and tolcapone, however no efficacy and safety data on this co-administration are currently available. COMT inhibitors increase the bioavailability of levodopa. Therefore, the dose of Hopledo may need to be decreased with concomitant use of COMT inhibitors.

Ferrous salts

Levodopa/carbidopa and ferrous salts or multivitamins containing ferrous salts should be co-administered with caution. Ferrous salts can form chelates with levodopa and carbidopa. Products containing ferrous sulphate and levodopa/carbidopa should be administered separately with the longest possible time interval between administrations (see section 4.2).

Alcohol interaction

No *in vivo* study was conducted for the effect of alcohol on treatment exposure. An *in vitro* dissolution study showed alcohol-induced dumping potential in the presence of 40% alcohol for levodopa. Dose dumping was not observed in the presence of lower alcohol concentrations.

Effect of levodopa and carbidopa on the metabolism of other medicinal products

Inhibition or induction effects of levodopa and carbidopa have not been investigated.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

Levodopa and possibly levodopa metabolites are excreted in human milk. There is evidence that lactation is suppressed during treatment with levodopa.

It is unknown whether carbidopa or its metabolites are excreted in human milk. Animal studies have shown excretion of carbidopa in breast milk.

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

Fertility

There are no data on the effects of levodopa or carbidopa on human fertility. No effects on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Levodopa has major influence on the ability to drive and use machines, as it may be associated with somnolence, sudden sleep episodes, dizziness and orthostatic hypotension. Therefore, caution should be exercised when driving or using machines while on treatment with Hopledo.

Patients presenting with somnolence and/or sudden sleep episodes must be advised to refrain from driving or engaging in activities where impaired alertness may put themselves 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

Summary of the safety profile

In a controlled clinical study, the most frequently reported ADRs were dyskinesia (7.6%), nausea (6.6%), dry mouth (4.6%) and dizziness (4.2%).

Serious events of psychiatric disorders (e.g. hallucination, delirium and psychotic disorders) were reported in the clinical studies with Hopledo. Gastrointestinal Haemorrhage and a symptom complex resembling neuroleptic malignant syndrome and rhabdomyolysis may occur with levodopa/carbidopa medicinal products, although no cases have been identified in clinical studies with Hopledo.

Tabulated list of adverse reactions

The table below includes all adverse reactions in clinical studies, as well as other similar combination products, where adverse reactions were considered related, presented by System Organ Class (SOC) and frequency.

Adverse reactions are ranked under headings of frequency using the following conventions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 2. Adverse reactions

System Organ Class	Very Common	Common	Uncommon	Unknown[a]
Infections and infestations	Urinary tract infection[a]			
Neoplasm benign, malignant and unspecified (including cysts and polyps)				Melanoma (see section 4.4)
Blood and lymphatic system disorders			Anaemia	Agranulocytosis, thrombocytopenia, leucopenia
Immune system disorders				Hypersensitivity
Metabolism and nutrition disorders		Decreased appetite, Vitamin B6 deficiency	Weight decreased	Weight increased
Psychiatric disorders		Confusional state, hallucination, depression (see section 4.5), anxiety, insomnia, sleep disorders	Psychotic episode, impulse control disorder (see section 4.4), abnormal dreams, agitation, illusion, bruxism	Suicidal ideation/attempt (see section 4.4), disorientation, dopaminergic dysregulation syndrome, euphoria
Nervous system disorders		Cognitive impairment, dizziness, dyskinesia, headache, worsening of Parkinson's disease, somnolence, gait disturbance	Convulsion, dystonia, trismus, syncope, restless legs syndrome, extrapyramidal disorder, muscle contraction involuntary, On and Off phenomenon, paraesthesia, tremor	Neuroleptic malignant syndrome (see section 4.3 and 4.4), sudden onset of sleep (see section 4.4), ataxia
Eye disorders		Vision blurred		Diplopia, mydriasis, oculogyric crises, activation of latent Horner's syndrome, blepharospasm

Cardiac disorders			Cardiac rhythm disorders[b] (see section 4.4), palpitations	
Vascular disorders		Orthostatic hypotension, hypotension (see section 4.4 and 4.9), hypertension (see section 4.5)		Thrombophlebitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Abnormal breathing pattern, hoarseness
Gastrointestinal disorders		Nausea, constipation, dry mouth, vomiting, abdominal pain,	Diarrhoea, dyspepsia, flatulence, dysphagia	Gastrointestinal haemorrhage, peptic ulcer disease (section 4.4), dysgeusia, glossodynia, dark saliva, hiccups, sialorrhoea
Skin and subcutaneous tissue disorders		Rash	Hot flush, hyperhidrosis, pruritis	Henoch-Schonlein purpura, urticaria (see section 4.3), hair loss, exanthema, dark sweat
Musculoskeletal and connective tissue disorders		Muscle spasms		
Renal and urinary disorders			Urinary retention	Dark urine, urinary incontinence
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions		Fall, fatigue	Peripheral oedema, asthenia, non-cardiac chest pain	Malaise
Investigations			Elevated creatinine Elevated alkaline phosphatases Leucocytes in the urine	Elevated urea nitrogen; positive Coomb's test; bacteria in the urine Elevated AST, ALT, LDH, bilirubin, blood sugar, uric acid; lowered values of haemoglobin and haematocrit; blood in urine

[a] Adverse reactions not observed in the controlled clinical study with Hopledo, but observed in non-controlled studies or reported for other levodopa/carbidopa medicinal products.

[b] Combined term that includes atrial fibrillation, bradycardia, atrioventricular block first degree, bundle branch block left, tachycardia, tachyarrhythmia

Description of selected adverse reactions

Sudden sleep onset

Hopledo is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Impulse control disorders
Pathological gambling, increased libido, 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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

The acute symptoms of levodopa/DDC inhibitor overdose can be expected to arise from dopaminergic overstimulation. Doses of a few grams may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g. hypotension, sinus tachycardia) and more severe psychiatric problems at higher doses. Levodopa overdose may give rise to systemic complications, secondary to dopaminergic overstimulation.

Treatment

Management of acute overdose with levodopa/DDC preparations is the same as management of acute overdose with levodopa. Pyridoxine is not effective in reversing the actions of this combination medicinal product. Electrocardiographic monitoring should be instituted and the patient should be observed carefully for the development of arrhythmias; if required, give appropriate antiarrhythmic therapy. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, dopaminergic agents, ATC code: N04BA02

Mechanism of action

Levodopa is a precursor of dopamine, and is given as dopamine replacement therapy in Parkinson's disease.

Carbidopa is a peripheral aromatic amino acid decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine exerts its therapeutic effects. A lower dose of levodopa can be used when it is co-administered with carbidopa, reducing the incidence and severity of peripheral side effects (nausea, vomiting).

Hopledo contains immediate-release granules and extended-release beads. The immediate-release granules consist of levodopa and carbidopa with a disintegrant polymer to allow for rapid dissolution. The extended-release beads consist of levodopa, coated with a sustained-release polymer to allow for slow release of the drug, a mucoadhesive polymer to keep the beads adhered to the area of absorption longer and an enteric coating to prevent the beads from disintegrating too early in the stomach.

Pharmacodynamic effects

At the maximum recommended dose, clinically significant QTc interval prolongation was not observed.

Clinical efficacy and safety

An active-control, multicentre Phase III clinical studies was performed with Hopledo in patients with Parkinson disease. It was a 20-week study consisting of a 3-week dose adjustment of current levodopa treatment prior to a 4-week conversion to Hopledo, which was followed by a 13-week, double-blind, double-dummy, randomised, parallel study group comparing Hopledo to immediate-release (IR) levodopa/carbidopa.

The study enrolled 630 (506 randomised) adult patients who had been maintained on a stable regimen of at least 400 mg per day of levodopa prior to entry into the study. Patients were continued on a stable dose of concomitant dopamine agonists (except apomorphine), selective monoamine oxidase B (MAO-B) inhibitors, amantadine, and anticholinergics provided the doses were stable for at least 4 weeks prior to screening.

During the dose-conversion period, 83 (14.1%) patients discontinued and were not randomised; only subjects who tolerated and responded to Hopledo were randomised. Patients were randomised to receive either IR levodopa/carbidopa or Hopledo at the dose determined during the adjustment or conversion phases.

Patients were not allowed to receive supplemental levodopa/carbidopa products, additional carbidopa or benserazide, any catechol-O-methyl transferase (COMT) inhibitor products, non-selective monoamine oxidase (MAO) inhibitors, selective MAO-A inhibitors, apomorphine, and antidopaminergic agents (including antiemetics) during the study.

In the study, most patients required 1 or 2 titration steps to reach a stable total daily dose of Hopledo. The dose strength or frequency of Hopledo was adjusted based on individual patient response to achieve the optimal balance of efficacy and tolerability. The final average dosing frequency was three times daily (TID) for Hopledo and five times daily for IR levodopa/carbidopa.

The majority (97%) of patients on Hopledo received 2400 mg or less; the mean dose was 1487 mg. The mean dose of IR levodopa/carbidopa was 862.7 mg.

The clinical outcome measure in the study was the mean change from baseline in “Good On” time in hours per day at the end of the study (Week 20 or at early termination), as assessed by the patient's Parkinson's Disease Diary, “Good On” time was defined as the sum of “on” time without dyskinesia and “on” time with non-troublesome dyskinesia.

Patients reported a statistically significant improvement in “Good On” time with Hopledo compared to IR levodopa/carbidopa, when Hopledo was dosed on average 3 times daily and IR levodopa/carbidopa was dosed on average 5 times daily. In the double-blind part of the study, Hopledo dosing frequency ranged from 2 to 4 times a day and IR levodopa/carbidopa dosing frequency ranged from 3 to 10 times a day. Hopledo-treated patients also reported significantly less "Off" time compared to IR levodopa/carbidopa.

In addition, significantly more Hopledo-treated patients were “much improved” or “very much improved” on the Patients' Global Impression of Change (PGIC) scale compared to IR levodopa/carbidopa.

Main study results are summarised in Table 3.

Table 3: Efficacy results of Hopledo versus IR levodopa/carbidopa in Parkinson's disease patients.

	Week 0 Enrolment	Week 7 Baseline	Week 20 End of study or early termination	p-value
Mean "Good On" time (h)				
Hopledo	9.46	11.67	11.35	0.0194*
IR levodopa/carbidopa	9.61	11.72	10.77	
Mean "Off" time (h)				
Hopledo	6.15	3.95	4.18	0.0252*
IR levodopa/carbidopa	6.05	4.02	4.75	
Percent of patients with either "much improved" or "very much improved" scores on PGIC scale				
Hopledo	N/A	N/A	29.7%	0.0015
IR levodopa/carbidopa	N/A	N/A	18.8%	

* p-value based on change from Week 7 (Baseline) to Week 20 (End of Study or Early Termination).

In patients aged 75 years and older the available clinical data do not allow a definitive assessment of potential differences in the clinical response of Hopledo compared with IR levodopa/carbidopa. In this age group, a higher rate of dopaminergic adverse events was observed. Those adverse events were generally mild to moderate in severity and transient. For these reasons, cautious dose conversion with close clinical monitoring is recommended (see section 4.2).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Hopledo in all subsets of the paediatric population in the treatment of Parkinson's disease,(see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of Hopledo were evaluated following single doses in healthy subjects and following single and multiple doses in patients with Parkinson's disease.

Levodopa
The bioavailability of levodopa from Hopledo in patients was approximately 85% relative to immediate-release levodopa/carbidopa.

For comparable doses, Hopledo results in a levodopa peak concentration (C_{max}) that is 38% that of immediate-release levodopa/carbidopa. Following an initial peak at about one hour, plasma concentrations are maintained for about 6 to 7 hours before declining.

In patients with Parkinson's disease, multiple-dose pharmacokinetics was comparable to single-dose pharmacokinetics, i.e., there was minimal accumulation of levodopa. Variation in levodopa peak to trough plasma concentrations at steady-state defined as $(C_{max}-C_{min})/C_{avg}$ was approximately 1.7 for Hopledo compared to approximately 2.8 for immediate-release levodopa/carbidopa.

Carbidopa
Following oral dosing of Hopledo, the maximum concentration occurred at approximately 2.5 hours. The bioavailability of carbidopa from Hopledo relative to immediate-release levodopa/carbidopa tablets was approximately 112%.

Effect of food

No specific recommendation is required regarding administration of Hopledo with food. Following administration with a high fat, high calorie meal, levodopa absorption is delayed, as reflected by a

substantially later Tmax and a marked reduction in early systemic exposure compared with the fasted state, while overall exposure is not reduced and is shifted to later time intervals.

Distribution

Levodopa
Levodopa is bound to plasma protein only to a small extent (10-30%). Levodopa crosses the blood-brain barrier by active transporters for large neutral amino acids. The apparent volume of distribution (V/F) of levodopa determined in clinical studies ranged between 83 and 164 L.

Carbidopa
Carbidopa is approximately 36% bound to plasma proteins. Carbidopa does not cross the blood-brain barrier at clinically relevant doses. The V/F of carbidopa determined in clinical studies ranged between 132 and 290 L.

Biotransformation and elimination

Levodopa
Levodopa is extensively metabolised to various metabolites. The two major metabolic pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT). Unchanged levodopa accounts for less than 10% of the total urinary excretion. The terminal phase elimination half-life of levodopa, the active moiety of antiparkinsonian activity, is approximately 2 hours in the presence of carbidopa.

In clinical studies, apparent clearance of levodopa ranged between 32 and 52 L/h.

Carbidopa
Carbidopa is metabolised to two main metabolites: α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxy-phenylpropionic acid. These two metabolites are primarily eliminated in the urine unchanged or as a glucuronide. Unchanged carbidopa accounts for 30% of the total urinary excretion. The terminal phase elimination half-life of carbidopa is approximately 2 hours. In clinical studies, apparent clearance of carbidopa ranged between 31 and 91 L/h.

Linearity

Hopledo shows dose proportional pharmacokinetics for both carbidopa and levodopa over the levodopa dosage strength range of 140 mg to 350 mg.

There are no clinically significant differences in the pharmacokinetic of levodopa or carbidopa based on gender, race, or body weight.

Elderly

In pharmacokinetic studies following a single dose of Hopledo, the peak concentrations of carbidopa and levodopa are generally similar between younger (45 to 60 years) and older (60 to 75 years) subjects. Pharmacokinetic characterisation in subjects older than 75 years is limited. No dose adjustment is needed for elderly patients (see section 4.2).

Renal and hepatic impairment

The pharmacokinetics of Hopledo in subjects with renal and/or hepatic impairment have not been established. Levodopa and carbidopa are primarily eliminated via non-renal routes. According to the population PK analysis done with extended-release levodopa/carbidopa, creatinine clearance is unlikely to have a clinically meaningful effect, given the minor contribution of estimated creatinine clearance to the variability in levodopa exposures. The magnitude of the effect for creatinine clearance above 30 mL/min is not considered clinically meaningful. Dose adjustment should be conducted with caution in patients with moderate to severe renal impairment and severe hepatic impairment.

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.

Reproductive toxicology

In reproduction studies, no effects on fertility were observed in rats receiving levodopa/carbidopa. Both levodopa and combinations of levodopa and carbidopa have caused visceral and skeletal malformations in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Microcrystalline cellulose
Mannitol
Sodium lauryl sulfate
Povidone
Cellulose acetate
Copovidone
Basic Butylated Methacrylate Copolymer
Talc (E553b)
Triethyl citrate (E1505)
Croscarmellose sodium
Magnesium stearate
Methacrylic Acid and Methyl Methacrylate Copolymer (1:1)

Capsule shell

Gelatine
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Quinoline yellow (E104)
Brilliant blue FCF (E133)
Erythrosine (E127)

Printing ink

Shellac glaze 45% (E904)
Ferrosoferric oxide/Iron oxide black (E172)
Propylene glycol (E1520)
Ammonium hydroxide 28% (E525)
Shellac NF (E904)
Sodium hydroxide (E524)
Povidone
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

100 days after first opening of the bottle.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

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

6.5 Nature and contents of container

Opaque, white, high-density polyethylene (HDPE) bottle with a white polypropylene (PP) child-resistant screw closure fitted with an induction inner-seal. Desiccant, silica gel in high-density polyethylene fiber packs, is included in the bottle.

Carton containing one bottle with 100 modified-release hard capsules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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fax: +39 02 66501492
e-mail: info.zambonspa@zambongroup.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2054/001

EU/1/26/2054/002

EU/1/26/2054/003

EU/1/26/2054/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Amneal EU Limited
Cahir Road, Cashel, Co Tipperary, E25 XD51, Ireland.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 140 mg/35 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 140 mg levodopa and 35 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule

100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.
Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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20091 Bresso (MI)
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tel: +39 02 665241
e-mail: info.zambonspa@zambongroup.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2054/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hopledo 140 mg/35 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/HDPE

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 140 mg/35 mg modified-release hard capsules

levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 140 mg levodopa and 35 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for furtehr information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule

100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2054/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 210 mg/52.5 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 210 mg levodopa and 52.5 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule
100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2054/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hopledo 210 mg/52.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/HDPE

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 210 mg/52.5 mg modified-release hard capsules

levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 210 mg levodopa and 52.5 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule

100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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EU/1/26/2054/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 280 mg/70 mg modified-release hard capsules

levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 280 mg levodopa and 70 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule
100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2054/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hopledo 280 mg/70 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/HDPE

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 280 mg/70 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 280 mg levodopa and 70 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for furtehr information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule
100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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EU/1/26/2054/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 350 mg/87.5 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 350 mg levodopa and 87.5 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule
100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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EU/1/26/2054/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hopledo 350 mg/87.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/HDPE

1. NAME OF THE MEDICINAL PRODUCT

Hopledo 350 mg/87.5 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release hard capsule contains 350 mg levodopa and 87.5 mg carbidopa (as monohydrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol. See leaflet for furtehr information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release hard capsule

100 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant. Do not eat.

8. EXPIRY DATE

EXP

After first opening the bottle, use within 100 days.

Date of first opening:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Hopledo 140 mg/35 mg modified-release hard capsules
Hopledo 210 mg/52.5 mg modified-release hard capsules
Hopledo 280 mg/70 mg modified-release hard capsules
Hopledo 350 mg/87.5 mg modified-release hard capsules
levodopa/carbidopa

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hopledo is and what it is used for

Hopledo contains the active substances levodopa and carbidopa, which belong to a class of medicines known as anti-Parkinson drugs.

Hopledo is used to treat moderate to severe alternating changes in the ability to move (motor fluctuations) in adults with Parkinson's disease when these cannot be adequately controlled by other medicines taken by mouth, belonging to a class of medicines called levodopa/dopa decarboxylase (DDC) inhibitor.

In people with Parkinson's disease, the cells in the brain that make a chemical messenger known as dopamine begin to die causing the amount of dopamine in the brain to decrease. The active substance in Hopledo, levodopa, increases dopamine in your body because the body converts levodopa into dopamine. This helps reduce the symptoms of Parkinson's disease. The other active substance in Hopledo, carbidopa, helps levodopa work better by stopping it from being broken down too early in the body, so more of it reaches the brain. This also reduces side effects allowing levodopa to be used more effectively.

2. What you need to know before you take Hopledo

Do not take Hopledo
- if you are allergic to levodopa, carbidopa or any of the other ingredients of this medicine (listed in section 6)
- if you have narrow-angle glaucoma, damage to the nerve in the eye caused by pressure inside the eye rising rapidly because fluid cannot drain out
- if you have pheochromocytoma, a rare tumour of the adrenal gland
- if you are taking certain medicines for treating depression called non-selective monoamine oxidase (MAO) inhibitors, such as phenelzine and isocarboxazid. Stop using these medicines at least two weeks before you start Hopledo (see also '**Other medicines and Hopledo**)

- if you have ever had neuroleptic malignant syndrome (NMS), a rare severe reaction to medicines used to treat severe mental disorders
- if you have ever had non-traumatic rhabdomyolysis, a rare muscle disorder.

Warnings and precautions
Talk to your doctor or pharmacist before or during use of Hopledo if one or more of the following applies to you:
- suddenly fall sleep or are very sleepy during daily activities
- have any form of severe mental disorder like psychosis
- have feelings of depression, thoughts of suicide, or notice unusual changes in your behaviour
- have chronic wide angle glaucoma, an eye condition in which increased pressure inside the eye gradually damages the nerve in the eye. Your dose may need to be adjusted and the pressure in your eyes may need to be monitored
- have melanoma, a type of skin cancer affecting cells called melanocytes, or suspicious skin lesion
- had a heart attack, blocked blood vessels in your heart or any other heart problems including irregular heartbeat, or circulation or breathing problems
- have kidney or liver problems
- have an ulcer in your gut (called ‘duodenal’ or ‘peptic ulcer’)
- have an endocrine (hormone) disease
- have bronchial asthma, a long-term condition in which the airways in your lungs become inflamed and narrowed. This can make it difficult to breathe and may cause wheezing, shortness of breath, chest tightness, and coughing
- have obsessive behaviour(s)
- have episodes of spasms and reduced consciousness (convulsions)
- feel dizzy or lightheaded on standing or sitting up because of a drop in blood pressure (orthostatic hypotension)
- have new or increased abnormal body movements (dyskinesias)
- develop urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or an increase in sexual thoughts or feelings
- you are aged 75 years or older. Your doctor should monitor you more closely, as you may be more sensitive to certain side effects of this medicine
- treatment with high doses of levodopa/carbidopa may lead to low levels of vitamin B6, which can increase the risk of seizures. If you are receiving high doses of this medicine, your doctor may perform blood tests to check your vitamin B6 levels. Tell your doctor if you experience signs of low levels of vitamin B6, such as pale skin, weakness or breathlessness (anemia), nerve pain or tingling in the hands and feet (polyneuropathy), or seizures

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Hopledo.

If you must undergo surgery, please tell your doctor that you are using Hopledo.

Do not stop using Hopledo unless your doctor tells you to. Suddenly stopping or lowering your Hopledo dose may cause a serious problem called neuroleptic malignant syndrome. This is characterised by fever, muscle stiffness, accelerated breathing, excessive sweating and changes in consciousness.

During treatment, regular heart, liver, kidney, and blood cell functions checks by the doctor are recommended. If you need to have tests on your blood or urine, tell the doctor or nurse that you are taking Hopledo. This is because the medicine may affect the results of some tests.

Children and adolescents

Hopledo should not be used in children and adolescents under 18 years as it has not been studied in this age group.

Other medicines and Hopledo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because other medicines can affect the way Hopledo works.

Do not take Hopledo if you have taken a medicine called a non-selective monoamine oxidase (MAO) inhibitor for treating depression in the last 14 days. These medicines include isocarboxazid and phenelzine. If this applies to you, do not take Hopledo and ask your doctor or pharmacist for advice.

In particular, tell your doctor or pharmacist if you are taking the following medicines:
- other medicines for Parkinson's disease, such as anticholinergics (e.g. orphenadrine and trihexyphenidyl), selective MAO-B inhibitors (e.g. selegiline, rasagiline and safinamide), and a COMT inhibitor (e.g. entacapone or opicapone)
- iron supplements or multivitamin supplements containing iron as levodopa/carbidopa may make it harder for your body to use iron. Therefore, do not take Hopledo and iron supplements or multivitamin supplements containing iron at the same time. After taking one of them, wait at least 2 to 3 hours before taking the other
- phenothiazines - such as chlorpromazine, promazine and prochloroperazine (used to treat mental illness)
- benzodiazepines such as alprazolam, diazepam, and lorazepam, used to treat anxiety
- tricyclic antidepressants (TCAs, used to treat depression)
- papaverine (used to improve blood flow around the body)
- treatment for high blood pressure (hypertension)
- phenytoin, which is used to treat seizures (convulsions)
- isoniazid, which is used to treat tuberculosis
- dopamine antagonists, used to treat mental disorders, nausea, and vomiting

Hopledo with food and drink
A high-fat, high-calorie meal delays the absorption of levodopa by 0.5-1 hour. If your diet is rich in protein (meat, eggs, milk, cheese), Hopledo may not work as well as it should. Avoid taking your capsules while having a high fat or high calorie meal.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Hopledo is not recommended during pregnancy and in women who can become pregnant who are not using effective contraception (birth control). However, your doctor may decide to give you Hopledo if the expected benefits of treatment outweigh possible risks to the unborn child.

It is not known if Hopledo passes into breast milk. Breast-feeding is not recommended during treatment with Hopledo.

Driving and using machines
Hopledo may have a major influence on the ability to drive and use machines. This is because Hopledo can cause somnolence (excessive drowsiness) and sudden sleep onset episodes.
Do not drive or use any tools or machines until you are sure how Hopledo affects you.
Do not drive, use tools or machines until you feel fully awake, or no longer feel light-headed or dizzy.

Hopledo contains propylene glycol
This medicine contains between 0.0024 and 0.0045 mg propylene glycol in each capsule.

3. How to take Hopledo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you exactly how many capsules of Hopledo to take each day.

If you have had levodopa before, your doctor will determine the appropriate starting dose regimen based on your current levodopa dose.

Hopledo should be taken approximately every 5-6 hours no more than 4 times per day.

Take this medicine by mouth with a glass of water. You must swallow your capsules whole. Do not break, crush or chew the capsules.

Alternatively, if you have difficulty swallowing a capsule, this medicine may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (e.g., 2 tablespoons) of soft food such as apple sauce. Do not heat the medicine/food mixture and do not sprinkle the contents of the capsule on hot food. Swallow the medicine/food mixture completely and immediately without chewing and do not store for future use.

Take the capsules at regular time intervals according to your doctor's instructions.

Do not change the times at which you take your capsules or take any other medicines for Parkinson's disease without first consulting your doctor.

Hopledo can be taken with or without food. Avoid taking your capsules with a high fat meal or one high calorie since this will delay the time it takes for the medicine to work.

Talk to your doctor or pharmacist if you think the effect of Hopledo is too strong or too weak, or if you experience possible side effects.

Depending on how you respond to treatment your doctor may either increase or decrease your dose and adjust your dosing frequency.

If you take more Hopledo than you should
If you take more Hopledo than you should (or someone has accidentally ingested Hopledo) seek medical attention immediately. In case of an overdose, you may feel confused or agitated, and your heart rate may be slower or faster than normal.

If you forget to take Hopledo
Take it as soon as you remember unless it is nearly time to take the next dose. Do not take a double dose to make up for a forgotten dose. Take the remaining doses at the correct time.

If you stop taking Hopledo
Do not stop taking Hopledo or change your dose without talking to your doctor first even if you feel better.

Do not stop taking Hopledo suddenly
This can cause muscle problems, fever and mental changes.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you have any of the following symptoms during your treatment with Hopledo, contact your doctor immediately:

- Bleeding in your stomach or intestines (gastrointestinal haemorrhage) which may be seen as blood in your faeces or darkened faeces.
- Swelling of the face, lips, tongue or throat (hypersensitivity) which makes it difficult to swallow or breathe, or nettle type skin rash.

- Your muscles get very rigid or jerk violently, you get tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in your blood pressure. These can be symptoms of a rare severe reaction to medicines used to treat disorders of the central nervous system (neuroleptic malignant syndrome (NMS)) or a rare severe muscle disorder (rhabdomyolysis).

Other possible side effects

Very common (may affect more than 1 in 10 people)
- infection of the parts of the body that collect and pass out urine (urinary tract infection)

Common (may affect up to 1 in 10 people)
- decreased appetite
- confusion
- behaviour disorder
- seeing or hearing things that are not real (hallucination)
- depression
- anxiety
- difficulty falling and/or staying asleep (insomnia)
- sleep disorders
- impaired memory and thinking skills (cognitive impairment)
- dizziness
- abnormal involuntary movements (dyskinesia)
- headache
- worsening of Parkinson’s disease
- sleepiness (somnolence)
- movement disorders (gait disturbances)
- blurred vision
- feeling dizzy or lightheaded on standing or sitting up because of a drop in blood pressure (orthostatic hypotension)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- feeling sick (nausea)
- constipation
- dry mouth
- belly (abdominal) pain
- vomiting
- rash
- muscle spasms
- falls
- tiredness (fatigue)
- Having too little vitamin B6

Uncommon (may affect up to 1 in 100 people)
- low levels of red blood cells (anaemia)
- weight decrease
- psychotic episode
- difficulty controlling actions or reactions (impulse control disorder)
- abnormal dreams
- agitation
- illusion
- grinding of the teeth (bruxism)
- convulsion
- twisting and repetitive movements or abnormal posture caused by involuntary muscle contraction (dystonia)
- difficulty opening the mouth (trismus)
- fainting (syncope)
- unpleasant sensations in the legs with an urge to move them (restless legs syndrome)

- involuntary movements (extrapyramidal disorder)
- involuntary muscle contraction
- on and off phenomenon, the time when your medicine is working and then it begins to no longer work to control your symptoms
- sensation of the skin that may feel like numbness, tingling, pricking, chilling, or burning (paraesthesia)
- tremor
- irregular heartbeat (cardiac rhythm disorder)
- forceful heartbeat that may be rapid or irregular (palpitations)
- shortness of breath (dyspnoea)
- diarrhoea
- indigestion (dyspepsia)
- excessive wind or gas (flatulence)
- difficulty swallowing (dysphagia)
- hot flush
- excessive sweating (hyperhidrosis)
- itch (pruritis)
- inability to completely empty the bladder of urine (urinary retention)
- swelling of the arms and/or legs (peripheral oedema)
- weakness (asthenia)
- chest pain unrelated to the heart (non-cardiac)
- increased creatinine levels
- increased alkaline phosphatase levels
- presence of white blood cells called leucocytes in the urine

Not known (frequency cannot be estimated from the available data)
- melanoma, a type of skin cancer
- a severe lack of neutrophils, a type of white blood cells (agranulocytosis)
- low levels of blood platelets (thrombocytopenia)
- low levels of white blood cell l (leucopenia)
- weight increase
- thoughts of suicide or suicide attempt
- disorientation
- craving for larger doses of Hopledo than required to control motor symptoms (dopamine dysregulation syndrome)
- euphoria
- sudden onset of sleep
- poor muscle control (ataxia)
- double vision (diplopia)
- pupil dilation (mydriasis)
- fixation of the eyeballs in one position (oculogyric crises)
- drooping eyelid, small pupil and decreased sweating on one side of the face (activation of latent Horner’s syndrome)
- eyelid twitching (blepharospasm)
- inflamed vein due to a blood clot (thrombophlebitis)
- Abnormal breathing pattern
- hoarseness
- peptic ulcer disease
- unusual taste in the mouth (dysgeusia)
- burning feeling of the tongue (glossodynia)
- dark saliva
- hiccups
- excessive drooling (sialorrhoea)
- a severe rash caused by inflamed blood vessels (Henoch-Schonlein purpura)
- hives
- hair loss
- rash (exanthema)

- dark sweat
- dark urine
- unintentional passing of urine (urine incontinence)
- prolonged and/or painful erection (priapism)
- feeling generally unwell (malaise)
- increased levels of certain liver or kidney markers (AST, ALT, LDH, bilirubin)
- increased levels of sugar
- increased levels of uric acid
- decreased levels of haemoglobin
- positive Coombs' test
- presence of bacteria in the urine
- presence of blood in the urine.

You may also experience the following side effects:
- Inability to resist the impulse to perform an action that could be harmful, which may include:
  - Strong impulse to gamble excessively despite serious personal or family consequences
  - Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - Uncontrollable excessive shopping or spending
  - Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these side effects; they will discuss ways of managing or reducing the symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hopledo

Keep this medicine out of the sight and reach of children.

Store in the original package due to sensitivity to moisture.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

After first opening the bottle, use within 100 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Hopledo contains

- The active substances are:
  - Hopledo 140 mg/35 mg modified-release hard capsules: each modified-release capsule contains 140 mg levodopa and 35 mg carbidopa (as monohydrate).
  - Hopledo 210 mg/52.5 mg modified-release hard capsules: each modified-release capsule contains 210 mg levodopa and 52.5 mg carbidopa (as monohydrate).
  - Hopledo 280 mg/70 mg modified-release hard capsules: each modified-release capsule contains 280 mg levodopa and 70 mg carbidopa (as monohydrate).
  - Hopledo 350 mg/87.5 mg modified-release hard capsules: each modified-release capsule contains 350 mg levodopa and 87.5 mg carbidopa (as monohydrate).

- The other ingredients are:
  Capsule content: croscarmellose sodium, povidone, magnesium stearate, cellulose, microcrystalline (E 460(i)), mannitol (E 421), sodium lauryl sulfate, cellulose acetate, copovidone, amino methacrylate copolymer, talc (E553b), triethyl citrate (E1505), methacrylic acid and methyl methacrylate copolymer (1:1).
  Capsule shell: gelatine, titanium dioxide, D&C yellow, red iron oxide, yellow iron oxide, FD&C blue #1 (E133) and FD&C red #3 (E127).
  Printing ink:
  Black imprinting ink: shellac glaze, black iron oxide, propylene glycol, ammonium hydroxide.
  White imprinting ink: shellac glaze, propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201), titanium dioxide (E171).

For information on excipients, see Section 2 “Hopledo contains propylene glycol”.

What Hopledo looks like and contents of the pack
Hopledo is a modified-release hard capsule.

Hopledo 140 mg/35 mg modified-release hard capsules
Hard capsules with white opaque body and yellow opaque cap. Body imprinted with "140" in black ink and cap imprinted with “IPX203” in white ink. Contains white to off-white granules and beads.

210 mg/52.5 mg modified-release hard capsule
Hard capsules with white opaque body and green opaque cap. Body imprinted with "210" in black ink and cap imprinted with “IPX203” in white ink. Contains white to off white granules and beads.

280 mg/70 mg modified-release hard capsule
Hard capsules with white opaque body and purple opaque cap. Body imprinted with "280" in black ink and cap imprinted with “IPX203” in white ink. Contains white to off-white granules and beads.

350 mg/87.5 mg modified-release hard capsule
Hard capsules with white opaque body and medium orange opaque cap. Body imprinted with "350'. in black ink and cap imprinted with “IPX203”' in white ink. Contains white to off-white granules and beads.

Hopledo capsules are supplied in plastic bottles with a desiccant and a plastic cap, with 100 modified-release capsules in each bottle. Each carton contains 1 bottle.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.