ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Numient 95 mg/23.75 mg modified-release hard capsules
Numient 145 mg/36.25 mg modified-release hard capsules
Numient 195 mg/48.75 mg modified-release hard capsules
Numient 245 mg/61.25 mg modified-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

95 mg/23.75 mg modified-release hard capsules
Each capsule contains 95 mg levodopa and 23.75 mg carbidopa (as monohydrate)

145 mg/36.25 mg modified-release hard capsules
Each capsule contains 145 mg levodopa and 36.25 mg carbidopa (as monohydrate)

195 mg/48.75 mg modified-release hard capsules
Each capsule contains 195 mg levodopa and 48.75 mg carbidopa (as monohydrate)

245 mg/61.25 mg modified-release hard capsules
Each capsule contains 245 mg levodopa and 61.25 mg carbidopa (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release hard capsule

95 mg/23.75 mg modified-release hard capsule
White body and a blue cap of 18 x 6 mm imprinted with “IPX066” and “95” in blue ink.

145 mg/36.25 mg modified-release hard capsule
Light blue body and a blue cap of 19 x 7 mm imprinted with “IPX066” and “145” in blue ink.

195 mg/48.75 mg modified-release hard capsule
Yellow body and a blue cap of 24 x 8 mm imprinted with “IPX066” and “195” in blue ink.

245 mg/61.25 mg modified-release hard capsule
Blue body and a blue cap of 23 x 9 mm imprinted with “IPX066” and “245” in blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of adult patients with Parkinson’s disease.

4.2 Posology and method of administration

Posology

Numient is recommended to be dosed orally, approximately every 6 hours. Dosing this medicinal product more than 5 times per day is not recommended.

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.

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

Initial dose and titration in levodopa-naïve patients

The starting dose is one capsule containing 95 mg of levodopa and 23.75 mg carbidopa three times daily (TID) for the first three days; this may be increased to a dose of one modified-release hard capsule containing 145 mg of levodopa and 36.25 mg carbidopa three times daily from Day 4 of treatment.

Further increases should be individualized based on clinical response. The daily dose must be determined by careful titration. Patients should be maintained on the lowest dose required to achieve symptomatic control and to minimize adverse reactions such as dyskinesia and nausea.

There is limited experience with a total daily dose of more than 1,170 mg of levodopa when administered in levodopa-naïve patients.

Converting patients from other levodopa/ dopa-decarboxylase (DDC) inhibitor (carbidopa or benserazide) immediate release medicinal products to Numient

As a result of Numient's pharmacokinetic characteristics, the doses and dosing frequency of Numient are not directly interchangeable with those of other levodopa/DDC inhibitor immediate release medicinal products (see section 5.2).

When patients are initially converted from immediate release levodopa/DDC inhibitor medicinal products to Numient, the dosing conversion guidelines provided in Table 1 are recommended for initial dosing.

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

Total daily dose of levodopa in immediate release levodopa/DDC inhibitor (mg)	**Initial total daily dose of Numient (levodopa in mg)**	**Suggested initial dose of Numient**
400 to 549	855	3 hard capsules 95 mg/23.75 mg TID
550 to 749	1140	4 hard capsules 95 mg/23.75 mg TID
750 to 949	1305	3 hard capsules 145 mg/36.25 mg TID
950 to 1249	1755	3 hard capsules 195 mg/48.75 mg TID
≥1250	2340	4 hard capsules 195 mg/48.75 mg TID
		or
	2205	3 hard capsules x 245 mg/61.25 mg TID

When patients are initially converted from immediate release levodopa/DDC inhibitor plus catechol-O-methyl transferase (COMT) inhibitors (such as entacapone) to Numient the dosing conversion guidelines provided in Table 2 are recommended for initial dosing.

Table 2: Guidelines for initial conversion from immediate release levodopa/DDC inhibitor plus catechol-O-methyl transferase (COMT) inhibitors (such as entacapone) to Numient in Parkinson's disease patients

Total daily dose of levodopa (mg) in levodopa/DDC inhibitor/entacapone	Initial total daily dose of Numient (levodopa in mg)	Suggested initial dose of Numient
400 to 549	1140	4 hard capsules 95 mg/23.75 mg TID
550 to 749	1470	2 hard capsules 245 mg/61.25 mg TID
750 to 949	1755	3 hard capsules 195 mg/48.75 mg TID
950 to 1249	2205	3 hard capsules 245 mg/61.25 mg TID
≥1250	2940	4 hard capsules 245 mg/61.25 mg TID

When converting patients from levodopa/DDC inhibitor medicinal products to Numient, the dose should be adjusted to maintain sufficient symptomatic control. The dosing frequency may be changed from three times a day to a maximum of five times a day if sufficient symptomatic control is not observed. In studies in advanced Parkinson's disease patients, there is limited data using doses above 2,450 mg of levodopa and 612.5 mg of carbidopa given as Numient.

The final total daily dose of levodopa from Numient is about double that of the final total daily dose of levodopa from immediate release tablets while the final total daily dose of levodopa from Numient is about three times that of the final total daily dose of levodopa from the combination of levodopa/DDC inhibitor/entacapone.

Converting patients specifically from other levodopa/DDC inhibitor modified-release medicinal products to Numient

For patients currently treated with other levodopa/DDC inhibitor modified-release medicinal products, limited information regarding conversion to Numient is available. The initial total daily dose of Numient described in Table 1 above may need to be decreased by approximately 30% for patients converting specifically from levodopa/DDC inhibitor modified-release medicinal products to Numient.

Maintenance

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

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

Modified-release levodopa/carbidopa 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 a symptom complex resembling neuroleptic malignant syndrome (NMS) have been associated 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 capsule medicinal product is required, especially if the patient is receiving antipsychotics (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, the usual dose should be administered as soon as the patient is able to take oral medicinal products.

Elderly

No dose adjustment of the modified-release levodopa/carbidopa medicinal product is required for elderly patients.

Renal impairment

Impact of renal function on levodopa/carbidopa clearance is limited (see section 5.2). Numient has not been studied in patients with renal impairment. It is recommended to administer this medicinal product cautiously to patients with severe renal disease (see section 4.4).

Hepatic impairment

Numient has not been studied in patients with hepatic impairment. It is recommended to administer this medicinal product cautiously to patients with severe hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Numient in children under 18 years of age have not been established. No data are available.

Method of administration

Numient should be administered with a glass of water and can be taken with or without food. A high-fat, high-calorie meal delays the absorption of levodopa by two hours. Further, high protein meals may impair clinical response by decreasing the absorption of levodopa (see section 4.5). Therefore, Numient should not be taken at the same time as high protein meals. The modified-release hard capsule should be swallowed whole, and not chewed or crushed, in order to maintain the modified-release effect of the levodopa/carbidopa medicinal product. Alternatively, for patients that have difficulty swallowing a capsule, this medicinal product 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, yoghurt, or pudding. The medicinal product/food mixture should be swallowed completely and immediately without chewing and should not be stored for future use. It cannot be excluded that heating may change the properties of the medicinal product. Therefore, the medicinal product should not be heated or added to hot food.

Products containing ferrous sulphate should be administered separately from levodopa/carbidopa, with the longest possible time interval between administrations (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Narrow-angle glaucoma.
- Phaeochromocytoma.
- Co-administration with non-selective monoamine oxidase (MAO) inhibitors. 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

CNS effects and mental disturbances

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.

Neuroleptic malignant syndrome (NMS)
Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of levodopa/carbidopa medicinal products. NMS is a life-threatening syndrome characterized by fever or hyperthermia and can be associated with rhabdomyolysis. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnoea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leucocytosis, myoglobinuria, and increased serum myoglobin have been reported. Therefore, patients must be monitored carefully when the dose of levodopa/carbidopa is reduced abruptly or discontinued, especially if the patient is receiving antipsychotics (see section 4.2).

Mental disturbances
Patients may experience new or worsening mental status and behavioural changes, which may be severe, including psychotic-like and suicidal behaviour during levodopa treatment or after starting or increasing the dose of levodopa. This abnormal thinking and behaviour can consist of one or more of a variety of manifestations including anxiety, depression, 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 levodopa/carbidopa because of the risk of exacerbating psychosis. In addition, certain medicinal products used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of levodopa/carbidopa. 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).

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

Dyskinesias
Medicinal products containing levodopa cause dyskinesias that may require treatment adjustment. Carbidopa permits more levodopa to reach the brain and more dopamine to be formed increasing the risk for certain adverse CNS reactions including dyskinesia. It is recommended to monitor patients for the onset or evolution of dyskinesia and to adjust levodopa/carbidopa doses accordingly.

Orthostatic hypotension
Levodopa/carbidopa can cause orthostatic hypotension. Levodopa/carbidopa should be used with caution in case of concomitant use of medicinal products that may cause orthostatic hypotension, e.g. anti-hypertensive medicinal products.

Glaucoma

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

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as medicinal products used to treat Parkinson's disease, is unclear.

For the reasons stated above, 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.

Laboratory testing

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.

Levodopa/carbidopa preparations may provide a false-positive test result for ketone bodies, if a test strip is used for determining any ketonuria. This reaction does not change upon boiling the urine sample. False negative results might be obtained upon application of glucose-oxidase methods for glucosuria.

Special populations

Levodopa/carbidopa should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastro-intestinal haemorrhage) and a history of convulsions.

Care should be exercised in administering levodopa/carbidopa to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dose adjustment.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors

Non-selective monoamine oxidase inhibitors must be discontinued at least 2 weeks prior to treatment initiation with the modified-release levodopa/carbidopa capsule medicinal product (see section 4.3). Numient can be taken concomitantly with the recommended dose of an MAO inhibitor, which is selective for MAO inhibitor type B such as selegiline and rasagiline. There is a recognized drug-drug interaction of levodopa with type B MAO inhibitors which potentiates the effects of levodopa. The combination may be associated with severe orthostatic hypotension.

The dose of levodopa may need to be reduced when an MAO inhibitor selective for type B is added. Patients should be maintained on the lowest dose required to achieve symptomatic control and to minimize adverse reactions.

Dopamine D2 receptor antagonists, benzodiazepines and isoniazid

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone), benzodiazepines and isoniazid may reduce the therapeutic effects of levodopa. Patients taking these medicinal products together with levodopa/carbidopa 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/carbidopa.

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 this modified-release levodopa/carbidopa medicinal product.

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

The effect of co-administration of this modified-release levodopa/carbidopa capsule product and COMT inhibitors such as entacapone has not been studied. The addition of entacapone to levodopa/carbidopa has been demonstrated to increase the levodopa bioavailability by 30%. The dose of the modified-release levodopa/carbidopa capsule medicinal product 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

In vivo, co-administration of Numient with up to 40% volume-to-volume (v/v) alcohol did not result in dose-dumping of levodopa or carbidopa.

Food interaction

In healthy adults, oral administration of Numient after a high-fat, high-calorie meal reduced levodopa C_{max} 21% while the overall extent of absorption of levodopa (AUC_{inf}) was similar (13% increase) to that observed in the fasted state (see section 5.2). Administration with a high-fat, high-calorie meal delays levodopa absorption by up to 2 hours (see section 4.2).

Following administration of the modified-release hard capsule contents sprinkled over a small quantity (e.g., 2 tablespoons) of soft food such as apple sauce, yoghurt, or pudding, the rate and extent of absorption of levodopa was similar to that observed in the fasted state.

Levodopa competes with certain amino acids for transport, therefore high protein meals may impair the absorption of levodopa.

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 or limited amount of data from the use of levodopa/carbidopa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Numient 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

Carbidopa is excreted in rat milk, but it is not known whether carbidopa or its metabolites are excreted in human breast milk. In a study of one breastfeeding mother with Parkinson's disease, excretion of levodopa in human milk was reported. There is insufficient information on the effects of levodopa/carbidopa or their metabolites in newborns/infants. Breast-feeding should be discontinued during treatment with Numient.

Fertility

There are no data on the effects of levodopa or carbidopa on human fertility. Effects of levodopa on fertility were evaluated in mouse studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Levodopa may have a major influence on the ability to drive and use machines. Certain side effects such as sleepiness and dizziness that have been reported with this modified-release levodopa/carbidopa capsule medicinal product may affect some patients' ability to drive or operate machinery.

Patients being treated with this modified-release levodopa/carbidopa capsule medicinal product and presenting with somnolence and/or sudden sleep episodes must be informed 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

The most frequently reported adverse reactions with Numient were nausea, occurring in approximately 12% of all patients; dizziness, headache, and dyskinesia, each occurring in approximately 8% of all patients; and insomnia, occurring in approximately 6% of all patients. Serious events of gastrointestinal haemorrhage (uncommon) and of allergic oedema (uncommon) were reported in the clinical studies with Numient. 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 Numient.

Tabulated list of adverse reactions

Adverse reactions are listed below by system organ class (SOC) and frequency (Table 3). Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency category, the adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions

	Adverse reactions observed in the clinical development of Numient			
System organ class	**Very Common**	**Common**	**Uncommon**	**Unknown[a)]**
Neoplasm benign, malignant and unspecified (including cysts and polyps)			Melanoma (see section 4.4)	
Blood and lymphatic system disorders			Anaemia	Agranulocytosis, thrombocytopenia, leucopenia
Metabolism and nutrition disorders		Weight decrease	Decreased appetite, weight increase	
Psychiatric disorders		Cognitive impairment, confusional state, hallucination, depression (see section 4.5), anxiety, abnormal dreams, insomnia	Psychotic episode, impulse control disorder (see section 4.4), agitation	Suicide attempt (see section 4.4), disorientation, dopaminergic dysregulation syndrome, euphoria, increased libido
Nervous system disorders		Dystonia, on and off phenomenon, dyskinesia, somnolence, gait disturbance, dizziness, worsening of Parkinson's disease, paraesthesia, headache, tremor	Convulsions, sudden onset of sleep (see section 4.4), trismus, restless legs syndrome	Neuroleptic malignant syndrome (see sections 4.3 and 4.4), ataxia
Eye disorders			Blurred vision, 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 (see section 4.4 and 4.9), hypertension (see section 4.5)	Syncope, thrombophlebitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Abnormal breathing pattern, hoarseness
Gastrointestinal disorders	Nausea	Abdominal pain, constipation, diarrhoea, dry mouth, vomiting	Gastrointestinal hemorrhage, peptic ulcer disease (see section 4.4), dysphagia, dyspepsia, dysgeusia, glossodynia, flatulence	Dark saliva, bruxism, hiccups, sialorrhoea
Skin and		Hot flushes,	Allergic oedema,	Henoch-Schönlein

	Adverse reactions observed in the clinical development of Numient			
System organ class	**Very Common**	**Common**	**Uncommon**	**Unknown[a)]**
subcutaneous tissue disorders		hyperhidrosis, rash (see section 4.3)	pruritus (see section 4.3)	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, peripheral oedema, non-cardiac chest pain, asthenia, fatigue	Malaise	
Investigations			Elevated AST, ALT, LDH, bilirubin, blood sugar, creatinine, uric acid; lowered values of haemoglobin and haematocrit; blood in urine	Elevated urea nitrogen, alkaline phosphatases; positive Coomb's test; leucocytes, and bacteria in the urine

a) Adverse reactions not observed in the clinical development of Numient, but reported for other levodopa/carbidopa medicinal products.

b) Combined term that includes atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block, sick sinus syndrome, bradycardia, and tachycardia

Description of selected adverse reactions

Sudden sleep onset

Numient 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).

Laboratory values

Cases of falsely diagnosed phaeochromocytoma in patients on levodopa/carbidopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or levodopa/carbidopa therapy.

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.

Pharmacodynamic effects

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for delivery to the brain. The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa.

Clinical efficacy and safety

Levodopa-naïve patients with Parkinson's disease
APEX-PD
The effectiveness of Numient in patients with early Parkinson's disease was established in a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group, 30-week clinical trial in 381 patients who had a median disease duration of 1 year and limited or no prior exposure to levodopa and dopamine agonists. Patients continued on stable concomitant anti-Parkinson medicinal product. Eligible patients were randomized (1:1:1:1) to placebo or one of three fixed levodopa/carbidopa doses of 145 mg/36.25 mg, 245 mg/61.25 mg, or 390 mg/97.5 mg, three times a day. Patients were not allowed to receive supplemental levodopa or catechol-O-methyl transferase (COMT) inhibitors. Patients receiving the modified-release levodopa/carbidopa medicinal product initiated treatment at 95 mg levodopa/23.75 mg carbidopa three times daily (TID). The dose was increased starting on Day 4 and the highest target dose (390 mg levodopa/97.5 mg carbidopa TID) was achieved by Day 22.

The primary efficacy endpoint was the mean change from baseline of the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (activities of daily living) score plus Part III motor score at week 30 or early termination. Each of the three modified-release levodopa/carbidopa treatments was statistically significantly superior to placebo on the primary measure (Table 4).

Table 4: Mean change from baseline in UPDRS Part II plus Part III score at week 30 (or at early termination) in levodopa naïve patients with Parkinson's disease (APEX-PD)

	Mean UPDRS (Part II and Part III) Score[a)]		
Treatment	**Baseline[b)]**	**Week 30 (or at early termination)**	**Change from baseline at week 30 (or at early termination)[c)]**
Placebo	36.5	35.9	−0.6
Numient 145 mg[d)]	36.1	24.4	−11.7 [e)]
Numient 245 mg[d)]	38.2	25.3	−12.9 [e)]
Numient 390 mg[d)]	36.3	21.4	−14.9 [e)]

a) For the UPDRS, higher scores indicate greater severity of impairment

b) All values based on 361 patients from the Intent to Treat population who had valid End of Study values

c) Negative numbers indicate improvement as compared with the baseline value

d) Three times per day

e) P-value is less than 0.05 versus placebo

Patients with advanced Parkinson's disease
The efficacy and safety of Numient in patients with advanced stage Parkinson's disease have been evaluated in 2 double-blind, active-controlled studies: parallel study ADVANCE-PD (study IPX066-B09-02; 22 weeks) and cross-over study ASCEND-PD (study IPX066-B-09-06 Part 1; 11 weeks).

In both studies the primary endpoint was the percentage "off" time during waking hours. The main secondary endpoints included "off" time, "on" time without troublesome dyskinesia, and UPDRS Parts II+III score. In the ADVANCE-PD study, the Clinical Global Impression of Change was also assessed.

ADVANCE-PD
The ADVANCE-PD study was a 22-week study consisting of a 3-week dose adjustment of pre-study immediate release levodopa/carbidopa treatment prior to a 6-week conversion to Numient. Next, patients were randomized to a double-blind, 13-week study treatment period of either optimized immediate release levodopa/carbidopa treatment or Numient. A total of 471 included patients had been maintained on a stable regimen of at least 400 mg per day of levodopa prior to entry into the trial. Dosing of concomitant anti-Parkinson medicinal products was kept stable. Patients were not allowed to receive supplemental levodopa/carbidopa or catechol-O-methyl transferase (COMT) inhibitor medicinal products during the trial. A total of 393 patients (mean age 63.2 years; 65% male patients) were randomized.

ASCEND-PD
The ASCEND-PD study was a randomized, double-blind, 2-treatment, 2-period crossover study in which 110 patients on a stable regimen of levodopa/carbidopa/entacapone (LCE) containing at least 400 mg per day of levodopa were included. Minimum dosing frequency was four times per day for at least 4 weeks upon entry into the trial. Concomitant anti-Parkinson medicinal products were kept stable during the study. LCE treatment was converted into Numient over a 6-week period. Following this dose conversion, 91 study patients (mean age: 64.1 years; 75% male patients) were randomized to receive Numient followed by pre-study LCE or vice versa. All efficacy data is based on 84 patients who completed the study with the exception of patient diary data which is based on 83. Each double-blind study period lasted 2 weeks. In between these periods, all patients received open-label Numient treatment for 1 week.

The most frequently recorded concomitant medicinal products for Parkinson's disease in randomized patients were dopamine agonists (64%), and MAO inhibitors (37%).

Results
Main study results are summarized in Table 5.

Table 5: Main results of studies in advanced Parkinson's disease

Study	**ADVANCE-PD**		**ASCEND-PD (cross-over)**	
Number of patients				
N entered	471		110	
N in conversion	450		110	
N randomised	393		91	
N completed	368		84	
Features of randomized patients				
Age [yrs (SD)]	63.2 (9.4)		64.1 (9.3)	
Duration PD [yrs (SD)]	7.4 (4.5)		10.0 (5.3)	
Outcomes				
Study arms	**Numient**	**IR L-dopa†**	**Numient**	**LCE**
	n=201	n=192	n=84	
Dose (mg), median (range)	1,330 (570; 5,390)	800 (400; 2,000)	1,495 (735; 4,900)	600 (400; 1,600)
Percentage "off" time*				
Baseline, mean	36.9%	36.0%	36.1%	
Endpoint, mean	23.8%	29.8%	24.0%	32.5%
Difference (95% CI)	-5.8% (-8.8; -2.7)		-8.6% (-12.4; -4.7)	
p-value	< 0.0001		< 0.0001	
"Off" time (hrs)*				
Baseline, mean	6.1	5.9	5.9	
Change at endpoint	-2.2	-1.0	-2.1	-0.7
Difference (95% CI)	-1.0 (-1.5; -0.5)		-1.4 (-2.1; -0.8)	
p-value	< 0.0001		< 0.0001	
"On" time without troublesome dyskinesia (hrs)*				
Baseline, mean	10.0	10.1	9.8	
Change at endpoint	+1.9	+0.8	+1.5	+0.1
Difference (95% CI)	1.0 (0.5; 1.5)		1.4 (0.7; 2.0)	
p-value	0.0002		< 0.0001	
$UPDRS_{II-III}$ score				
Baseline, mean	32.3	32.4	32.0	
Change at endpoint	-5.7	-2.1	-2.7	-0.3
Difference (95% CI)	-4.0 (-5.9; -2.0)		-2.6 (-4.8; -0.4)	
p-value	< 0.0001		0.0233	
Responder analyses				
≥1 hour improvement in "off" time (95% CI)	63.2% (56.5; 69.9)	45.3% (38.3; 52.4)	64.0% (54.1; 74.0)	50.0% (39.6; 60.5)
p-value	< 0.0001		0.0094	
CGI-C much improved (95% CI)	40.0% (33.2; 46.8)	13.7% (8.8; 18.6)	N/A	N/A
p-value	< 0.0001		N/A	

Abbreviations: CGI-C: clinical global impression of change from baseline; CI: confidence interval; IR: immediate release; LCE: Levodopa/Carbidopa/Entacapone; L-dopa†: Levodopa/Carbidopa; LS: least squares; PD: Parkinson's disease; SD: standard deviation; N/A: not available; hrs: hours; yrs: years.

*In the ADVANCE-PD study an Analysis of Covariance (ANCOVA) model for End of Study was used with treatment and centres as main effects and interaction term for treatment by centre and baseline as covariate.

Data in the ASCEND-PD study were analysed using a standard mixed-model analysis of variance. Treatment, sequence and period were included as fixed effects, intra- and inter subject factors were included as random effects. There was no evidence of period, sequence/carry-over effects in the ASCEND-PD study (p-values all > 0.10).

Paediatric population

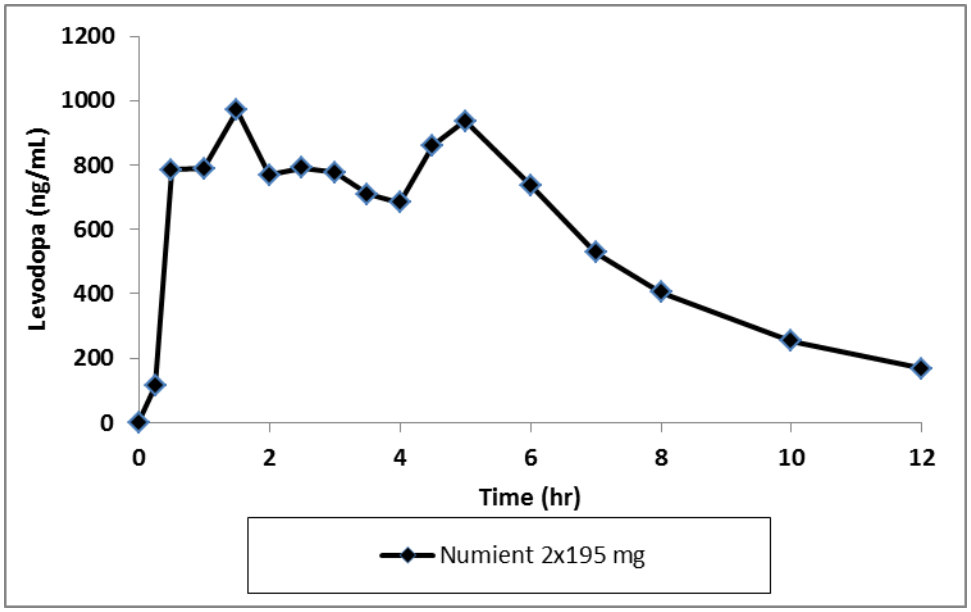
The European Medicines Agency has waived the obligation to submit the results of studies with Numient in all subsets of the paediatric population in the treatment of idiopathic Parkinson's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Levodopa
The pharmacokinetics of Numient were evaluated following single doses in healthy subjects and following single and multiple doses in patients with Parkinson's disease. The single dose pharmacokinetics in healthy adults following oral administration of 2 Numient 195 mg levodopa/48.75 mg carbidopa capsules is presented in Figure 1.

Figure 1: Mean concentration-time profiles of levodopa plasma concentrations in 22 adults following a single oral dose of 2 Numient 195 mg levodopa/48.75 mg carbidopa capsules



The bioavailability of levodopa from Numient in patients was approximately 70% relative to immediate release levodopa/carbidopa. For comparable doses, Numient results in a levodopa peak concentration (C_{max}) that is 30% that of immediate-release levodopa/carbidopa. Following an initial peak at about one hour, plasma concentrations are maintained for about 4 to 5 hours before declining. Peak plasma concentrations are reached at about 4.5 hours. In patients with Parkinson's disease, multiple-dose pharmacokinetics was comparable to single-dose pharmacokinetics, i.e. there was a minimal accumulation of levodopa from the modified-release levodopa/carbidopa medicinal product.

Following multiple dosing in patients, modified-release levodopa/carbidopa had reduced fluctuations in levodopa plasma concentrations with peak-to-trough fluctuation index of 1.5 with minimal accumulation of levodopa.

Carbidopa
Following oral dosing of the modified-release levodopa/carbidopa medicinal product the maximum concentration occurred at approximately 3.5 hours. The bioavailability of carbidopa from this medicinal product relative to immediate release levodopa and carbidopa tablets was approximately 50%.

Food effect

In healthy adults, oral administration of the modified-release levodopa/carbidopa medicinal product after a high-fat, high-calorie meal reduced levodopa C_{max} by 21%. The extent of absorption of levodopa (AUC_{inf}) was similar (13% increase) to that observed in the fasted state. Administration with a high-fat, high-calorie meal delays levodopa absorption by up to 2 hours.

Following administration of the modified-release hard capsule contents sprinkled over a small quantity of soft food such as apple sauce, the rate and extent of absorption of levodopa was similar to that observed in the fasted state.

Levodopa competes with certain amino acids for transport, therefore high protein meals may impair the absorption of levodopa.

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.

Carbidopa
Carbidopa is approximately 36% bound to plasma proteins. Carbidopa does not cross the blood-brain barrier at clinically relevant doses.

Biotransformation

Levodopa
Levodopa is extensively metabolized 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.

Carbidopa
Carbidopa is metabolized 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 glucuronide. Unchanged carbidopa accounts for 30% of the total urinary excretion. The terminal phase elimination half-life of carbidopa is approximately 2 hours.

Dose linearity

Numient shows dose proportional pharmacokinetics for both carbidopa and levodopa over the levodopa dose strength range of 95 mg to 245 mg.

Renal impairment

Renal excretion of intact levodopa accounts for only about 10% of clearance. Thus, impaired renal function may potentially have a small effect on the exposure of levodopa. Modified-release levodopa/carbidopa should be administered cautiously to patients with severe renal impairment (see section 4.2).

Hepatic impairment

There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with hepatic impairment (see section 4.2). Modified-release levodopa/carbidopa should be administered cautiously to patients with severe hepatic impairment.

Paediatric population

There are no studies on the pharmacokinetics of levodopa and carbidopa when administered as Numient in children.

Elderly

In the pharmacokinetic studies conducted in patients following a single dose of Numient, systemic exposure to levodopa generally increased with increasing age with AUC values being, on average, approximately 15% higher in elderly (≥65 years) than younger subjects (<65 years).

Gender

Levodopa
Following a single dose of Numient in patients with Parkinson's disease the plasma AUC and C_{max} of levodopa was higher in females than males (on average, 37% for AUC and 35% for C_{max}). These differences are primarily explained by the lower body weight in females.

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, and carcinogenic potential.

Reproductive toxicology

Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits.

No effects were seen on male or female reproductive organs in repeat dose toxicology studies in mice, rats or monkeys with levodopa alone, or in combination with carbidopa. However, levodopa has been shown to mildly affect mating behaviour in male rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Cellulose, microcrystalline
Mannitol
Tartaric acid
Ethylcellulose
Hypromellose
Sodium starch glycolate
Sodium laurilsulfate
Povidone
Talc
Methacrylic acid – methyl methacrylate copolymers (1:1)
Methacrylic acid – methyl methacrylate copolymers (1:2)
Triethyl citrate
Croscarmellose sodium
Magnesium stearate

Capsule shell

Indigo carmine (E132), lake
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatine

Ink

SB-6018 blue ink
Shellac (E904)
Propylene glycol
Indigo carmine (E132), lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

90 days after first opening.

6.4 Special precautions for storage

Store below 30 °C. Store in the original package in order to protect from light and 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 polypropylene screw closure. Desiccant is included in the bottle.

One bottle containing 25, 100 or 240 modified-release hard capsules.

Not all pack sizes may be marketed.

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

Impax Laboratories Ireland Limited
56 Fitzwilliam Square
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBERS

Numient 95 mg/23.75 mg modified-release hard capsules

EU/1/15/1044/001 (25 modified-release hard capsules)
EU/1/15/1044/002 (100 modified-release hard capsules)
EU/1/15/1044/003 (240 modified-release hard capsules)

Numient 145 mg/36.25 mg modified-release hard capsules

EU/1/15/1044/004 (25 modified-release hard capsules)
EU/1/15/1044/005 (100 modified-release hard capsules)
EU/1/15/1044/006 (240 modified-release hard capsules)

Numient 195 mg/48.75 mg modified-release hard capsules

EU/1/15/1044/007 (25 modified-release hard capsules)
EU/1/15/1044/008 (100 modified-release hard capsules)
EU/1/15/1044/009 (240 modified-release hard capsules)

Numient 245 mg/61.25 mg modified-release hard capsules

EU/1/15/1044/010 (25 modified-release hard capsules)
EU/1/15/1044/011 (100 modified-release hard capsules)
EU/1/15/1044/012 (240 modified-release hard capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015

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

Central Pharma Contract Packing Limited
Caxton Road, Bedford, Bedfordshire
MK41 0XZ
United Kingdom

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**

The requirements for submission of periodic safety update reports 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 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

BOX/CARTON

1. NAME OF THE MEDICINAL PRODUCT

Numient 95 mg/23.75 mg modified-release hard capsules
Numient 145 mg/36.25 mg modified-release hard capsules
Numient 195 mg/48.75 mg modified-release hard capsules
Numient 245 mg/61.25 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 95 mg of levodopa and 23.75 mg of carbidopa (as monohydrate).
Each capsule contains 145 mg of levodopa and 36.25 mg of carbidopa (as monohydrate)
Each capsule contains 195 mg of levodopa and 48.75 mg of carbidopa (as monohydrate)
Each capsule contains 245 mg of levodopa and 61.25 mg of carbidopa (as monohydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

25 modified-release hard capsules
100 modified-release hard capsules
240 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow whole, 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

8. EXPIRY DATE

EXP
After opening the bottle, use within 90 days.

Opened:

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C. Store in the original package, in order to protect from light and 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

Impax Laboratories Ireland Limited
56 Fitzwilliam Square
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

Numient 95mg/23.75 mg modified-release hard capsules
EU/1/15/1044/001 (25 modified-release hard capsules)
EU/1/15/1044/002 (100 modified-release hard capsules)
EU/1/15/1044/003 (240 modified-release hard capsules)

Numient 145 mg/36.25 mg modified-release hard capsules
EU/1/15/1044/004 (25 modified-release hard capsules)
EU/1/15/1044/005 (100 modified-release hard capsules)
EU/1/15/1044/006 (240 modified-release hard capsules)

Numient 195 mg/48.75 mg modified-release hard capsules
EU/1/15/1044/007 (25 modified-release hard capsules)
EU/1/15/1044/008 (100 modified-release hard capsules)
EU/1/15/1044/009 (240 modified-release hard capsules)

Numient 245 mg/61.25 mg modified-release hard capsules
EU/1/15/1044/010 (25 modified-release hard capsules)
EU/1/15/1044/011 (100 modified-release hard capsules)
EU/1/15/1044/012 (240 modified-release hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Numient 95/23.75 mg
Numient 145/36.25 mg
Numient 195/48.75 mg
Numient 245/61.25 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/HDPE

1. NAME OF THE MEDICINAL PRODUCT

Numient 95 mg/23.75 mg modified-release hard capsules
Numient 145 mg/36.25 mg modified-release hard capsules
Numient 195 mg/48.75 mg modified-release hard capsules
Numient 245 mg/61.25 mg modified-release hard capsules
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 95 mg of levodopa and 23.75 mg of carbidopa (as monohydrate)
Each capsule contains 145 mg of levodopa and 36.25 mg of carbidopa (as monohydrate)
Each capsule contains 195 mg of levodopa and 48.75 mg of carbidopa (as monohydrate)
Each capsule contains 245 mg of levodopa and 61.25 mg of carbidopa (as monohydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

25 modified-release hard capsules
100 modified-release hard capsules
240 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow whole, 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

8. EXPIRY DATE

EXP
After opening the bottle, use within 90 days.

Opened:

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C. Store in the original package, in order to protect from light and 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

Impax logo

12. MARKETING AUTHORISATION NUMBER(S)

Numient 95mg/23.75 mg modified-release hard capsules
EU/1/15/1044/001 (25 modified-release hard capsules)
EU/1/15/1044/002 (100 modified-release hard capsules)
EU/1/15/1044/003 (240 modified-release hard capsules)

Numient 145 mg/36.25 mg modified-release hard capsules
EU/1/15/1044/004 (25 modified-release hard capsules)
EU/1/15/1044/005 (100 modified-release hard capsules)
EU/1/15/1044/006 (240 modified-release hard capsules)

Numient 195 mg/48.75 mg modified-release hard capsules
EU/1/15/1044/007 (25 modified-release hard capsules)
EU/1/15/1044/008 (100 modified-release hard capsules)
EU/1/15/1044/009 (240 modified-release hard capsules)

Numient 245 mg/61.25 mg modified-release hard capsules
EU/1/15/1044/010 (25 modified-release hard capsules)
EU/1/15/1044/011 (100 modified-release hard capsules)
EU/1/15/1044/012 (240 modified-release hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Numient 95 mg/23.75 mg modified-release hard capsules

Numient 145 mg/36.25 mg modified-release hard capsules

Numient 195 mg/48.75 mg modified-release hard capsules

Numient 245 mg/61.25 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 Numient is and what it is used for

Numient contains two different medicines called levodopa and carbidopa in one hard capsule.
- levodopa turns into a material called 'dopamine' in your brain. The dopamine helps to improve the symptoms of your Parkinson's disease.
- carbidopa belongs to a group of medicines called 'aromatic amino acid decarboxylase inhibitors'. It helps levodopa work more effectively by slowing the speed at which levodopa is broken down in your body.

Numient is used to improve the symptoms of Parkinson's disease in adults.

2. What you need to know before you take Numient

Do not take Numient:

- if you are allergic to levodopa or carbidopa, or any of the other ingredients of this medicine (listed in section 6);
- if you have narrow-angle glaucoma (an eye disorder);
- if you have phaeochromocytoma (a rare tumour of the adrenal gland);
- if you are taking certain medicines for treating depression [non-selective monoamine oxidase (MAO) inhibitors]. You need to stop using these medicines at least two weeks before you start Numient (see also under '**Other medicines and Numient**');
- 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 taking Numient if you have, have ever had, or develop:
- sudden sleep attacks or sometimes feel very sleepy
- any form of severe mental disorder like psychosis
- feelings of depression, suicidal thoughts, or notice unusual changes in your behaviour
- tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in your blood pressure, or notice that your muscles get very rigid or jerk violently. If any of this happens, **contact your doctor immediately**
- an eye condition called chronic wide angle glaucoma, because your dose may need to be adjusted and the pressure in your eyes may need to be monitored
- melanoma or suspicious skin lesion
- a heart attack, heart beat problems, circulation or breathing problems
- kidney or liver problems
- an ulcer in your gut (called 'duodenal' or 'peptic ulcer')
- an endocrine (hormone) disease
- bronchial asthma
- obsessive behaviour(s)
- convulsions
- low blood pressure or feeling dizzy when getting up
- new or increased abnormal body movements (dyskinesias)

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

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

Impulse control disorders
Tell your doctor if you or your family/carer notices you are developing 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. Your doctor may need to review your treatments.

Tests
You may need to have testing of your heart, liver, kidney, and blood cell functions during long-term treatment with medicines containing levodopa/carbidopa. If you need to have tests on your blood or urine, tell the doctor or nurse that you are taking Numient. This is because the medicine may affect the results of some tests.

Children and adolescents

The use of Numient is not recommended in patients under 18 years of age. The safety and efficacy of Numient in patients under 18 years of age have not been studied

Other medicines and Numient

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 Numient works.

Do not take Numient 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 Numient 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 and rasagiline), and a 'COMT inhibitor' (e.g. entacapone)
- Ferrous sulphate (used to treat anaemia caused by low levels of iron in the blood). Levodopa/carbidopa may make it harder for your body to use iron. Therefore, do not take Numient 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 fits (convulsions)
- Isoniazid which is used to treat tuberculosis
- Dopamine antagonists used to treat mental disorders, nausea, and vomiting

Numient with food and drink

A high-fat, high-calorie meal delays the absorption of levodopa by two hours. If your diet contains too much protein (meat, eggs, milk, cheese), Numient may not work as well as it should. Avoid taking your capsules at the same time that you consume a high fat or high protein meal.

Pregnancy, breast-feeding, and fertility

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 Numient.

Numient is not recommended during pregnancy and in women of childbearing potential not using contraception. However, your doctor may decide to give you Numient if the expected benefits of treatment outweigh possible risks to the unborn child.

Women should not breast-feed during treatment with Numient.

Driving and using machines

Numient can cause somnolence (excessive drowsiness) and sudden sleep onset episodes. Therefore, you must refrain from driving or engaging in activities where impaired alertness may put yourself or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved.

3. How to take Numient

- 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 Numient to take each day
- If you have never had levodopa before, the usual starting dose for Numient is one 95 mg capsule three times a day for three days. Depending on how you respond to treatment your doctor may then increase your dose on day four
- If you have had levodopa before, your doctor will determine the appropriate starting dose regimen based on your current levodopa dose
- Numient should be taken approximately every 6 hours no more than 5 times a 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, yoghurt, or pudding. 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. You should not take Numient capsules at intervals of less than 4 hours apart
- Numient can be taken with or without food. Avoid taking your capsules with a high fat meal or one high in protein 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 Numient is too strong or too weak, or if you experience possible side effects
- Depending on how you respond to treatment your doctor may then either increase or decrease your dose and adjust your dosing frequency

If you take more Numient than you should

If you take more Numient than you should (or someone has accidentally ingested Numient) talk to your doctor or pharmacist 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 a dose of Numient

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 Numient

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

Do not stop taking Numient 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 Numient, **contact your doctor immediately:**

- Bleeding in your stomach or intestines which may be seen as blood in your faeces or darkened faeces
- An allergic reaction, the signs of which may include hives (nettle rash), itching, rash, swelling of your face, lips, tongue or throat. This may cause difficulties in breathing or swallowing
- 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 neuroleptic malignant syndrome (NMS, a rare severe reaction to medicines used to treat disorders of the central nervous system) or rhabdomyolisis (a rare severe muscle disorder)

Other possible side effects:
Very common (may affect more than 1 in 10 people)
- Feeling sick to your stomach (nausea)

Common (may affect up to 1 in 10 people)
- Decrease in weight
- Seeing or hearing things that are not real, depression, anxiety, somnolence (excessive drowsiness), difficulty falling and/or staying asleep, abnormal dreams, confusion, impaired memory and thinking skills
- Twisting and repetitive movements or abnormal posture caused by involuntary muscle contraction (dystonia), abnormal involuntary movements (dyskinesia), on and off phenomenon (the time when your medicine is working and then it begins to no longer work to control your symptoms), worsening of Parkinsons's disease, abnormal walking, dizziness, excessive drowsiness, prickling or tingling feeling in your arms and/or legs, tremor, headache
- Irregular heart rhythm
- High blood pressure, abnormally low blood pressure when you stand up
- Shortness of breath
- Abdominal pain, constipation, diarrhoea, dry mouth, vomiting
- Hot flushes, excessive sweating, rash
- Muscle spasms
- Falls
- Swelling of the arms and/or legs
- Chest pain not due to heart disease
- Loss of strength, fatigue

Uncommon (may affect up to 1 in 100 people)
- Melanoma (a type of skin cancer)
- Anaemia (low red blood cell counts)
- Decreased appetite, increased weight
- Psychotic episode, agitation
- Impulse control disorder (see below)
- Sudden sleep onset episodes, restless legs syndrome (unpleasant sensations in the legs with an urge to move them), difficulty opening the mouth, convulsions
- Double vision, dilated pupils, blurred vision
- Pounding heartbeat
- Fainting, blood clot or inflammation in a blood vessel
- Bleeding in the stomach or intestines, peptic ulcer disease, difficulty swallowing, indigestion, unusual taste in the mouth, burning feeling of the tongue, excessive wind or gas (flatulence)
- An allergic reaction, which may include hives (nettle rash), itching, rash, swelling of your face, lips, tongue or throat, difficulty breathing or swallowing, itching
- Inability to urinate
- General feeling of illness (malaise)
- Increased levels of sugar, uric acid and/or liver enzymes in the blood
- Abnormal kidney function tests and/or 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 behaviours; they will discuss ways of managing or reducing the symptoms.

The following side effects have also been reported but the chance that they will occur is unknown:
- Low blood cell counts (white blood cells, platelets)
- Drug abuse of certain medicines used to treat Parkinson's Disease
- Suicide attempt, feeling disoriented, increased sexual feelings
- Severe prolonged abnormal eye movements, Horner's Syndrome (drooping eyelid, small pupil and decreased sweating on one side of the face), eyelid twitching
- Abnormal breathing pattern
- Excessive or dark-coloured saliva, grinding of the teeth, hiccups
- Hair loss, rash (including a severe rash called Henoch-Schönlein purpura), dark-coloured sweat

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 Numient

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

Store below 30 °C. Store the medicine in the original package, in order to protect from light and moisture.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month. After opening the bottle, use within 90 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 Numient contains

- The active substances of Numient are levodopa and carbidopa
  - Each 95 mg/23.75 mg modified-release hard capsule contains 95 mg levodopa and 23.75 mg carbidopa (as monohydrate)
  - Each 145 mg/36.25 mg modified-release hard capsule contains 145 mg levodopa and 36.25 mg carbidopa (as monohydrate)
  - Each 195 mg/48.75 mg modified-release hard capsule contains 195 mg levodopa and 48.75 mg carbidopa (as monohydrate)
  - Each 245 mg/61.25 mg modified-release hard capsule contains 245 mg levodopa and 61.25 mg carbidopa (as monohydrate)

- The other ingredients are cellulose, microcrystalline, mannitol, tartaric acid, ethylcellulose, hypromellose, sodium starch glycolate, sodium laurilsulfate, povidone, talc, methacrylic acid – methyl methacrylate copolymers (1:1), methacrylic acid – methyl methacrylate copolymers (1:2), triethyl citrate, croscarmellose sodium and magnesium stearate

- The ingredients in the hard capsule shell are indigo carmine (E132) lake, yellow iron oxide (E172), titanium dioxide (E171) and gelatine

- The ingredients in the ink are SB-6018 blue ink, shellac (E904), propylene glycol, and indigo carmine (E132) lake

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

95 mg/23.75 mg modified-release hard capsule
White body and a blue cap of 18 x 6 mm imprinted with “IPX066” and “95” in blue ink.

145 mg/36.25 mg modified-release hard capsule
Light blue body and a blue cap of 19 x 7 mm imprinted with “IPX066” and “145” in blue ink.

195 mg/48.75 mg modified-release hard capsule
Yellow body and a blue cap of 24 x 8 mm imprinted with “IPX066” and “195” in blue ink.

245 mg/61.25 mg modified-release hard capsule
Blue body and a blue cap of 23 x 9 mm imprinted with “IPX066” and “245” in blue ink.

Numient capsules are supplied in plastic bottles with a dessicant and a plastic cap, available in bottles of 25, 100 or 240 hard capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Impax Laboratories Ireland Limited
56 Fitzwilliam Square
Dublin 2
Ireland

Manufacturer

Central Pharma Contract Packing Limited
Caxton Road, Bedford, Bedfordshire
MK41 0XZ
United Kingdom
44(0) 1234 227816

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Other sources of information

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