SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Inbrija 33 mg inhalation powder, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 42 mg levodopa.

Each delivered dose contains 33 mg levodopa.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

White opaque capsules containing white powder, with “A42” printed in black on the cap of the capsule and two black bands printed on the body of the capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Inbrija is indicated for the intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson’s disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor.

4.2 Posology and method of administration

Posology

Patients should be on a stable levodopa/dopa-decarboxylase inhibitor (e.g. carbidopa or benserazide) regimen before starting Inbrija.

Patients selected for treatment with Inbrija should be able to recognize the onset of their 'OFF' symptoms and be capable of preparing the inhaler or else have a responsible care giver able to prepare the inhaler for them when required.

Inbrija should be inhaled when symptoms, motor or non-motor, of an OFF period start to return.

The recommended dose of Inbrija is 2 hard capsules up to 5 times per day each delivering 33 mg levodopa. The maximum daily dose of Inbrija should not exceed 10 capsules (330 mg). It is not recommended to take more than 2 capsules per OFF period. Exceeding the recommended dose may lead to increased levodopa associated adverse reactions.

Abrupt dose reduction or withdrawal of any levodopa medicinal product should be carefully observed, particularly in patients who are also receiving neuroleptics. See section 4.4 regarding withdrawal emergent hyperpyrexia and confusion.

Elderly

No dose adjustment of Inbrija is required for elderly patients (≥65 years). There is only limited data available in very elderly patients (≥75 years).

Renal impairment

Inbrija has not been studied in patients with renal impairment. It is recommended to administer this medicinal product cautiously to patients with severe renal disease.

Hepatic impairment

Inbrija has not been studied in patients with hepatic impairment. It is recommended to administer this medicinal product cautiously to patients with severe hepatic impairment.

Paediatric population

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

Method of administration

For inhalation use only. Inbrija hard capsules must not be swallowed.

The Inbrija inhaler is to be thrown away after all the capsules have been used.

The capsules must only be removed from the blister immediately before use.

The physician or other healthcare professional should instruct the patient how to administer the product correctly. A summary of how to use Inbrija is provided below.

- A complete dose is 2 capsules taken one right after the other.
- The patient should load 1 capsule into the Inbrija inhaler, breathe in and hold their breath for 5 seconds. The patient should hear the capsule “whirl”.
- The used capsule should be removed from the Inbrija inhaler and the second capsule loaded into the inhaler. The maximum time between inhalation of the powder from the first and second capsules should not exceed 10 minutes.
- It is important to advise the patient that if they do not hear or feel the capsule “whirl” while inhaling they may need to take a deeper, longer breath, breathing in again using the same capsule or they may need to clean the mouthpiece.

Detailed instructions for use for the patients are included in the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance 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 should already be discontinued for at least two weeks prior to initiating therapy due to the established underlying levodopa 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

Bronchospasm in patients with lung disease

Because of the risk of bronchospasm, use of levodopa inhalation powder in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended. There is limited data regarding chronic effect of Inbrija in respiratory compromised patients.

Central Nervous System (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.

Withdrawal-emergent 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 changes in the background dopaminergic therapy. Therefore, any abrupt dose reduction or withdrawal of any levodopa medicinal product should be carefully observed, particularly in patients who are also receiving neuroleptics.

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 a levodopa/dopa-decarboxylase inhibitor 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. 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 can occur in patients treated with levodopa. Review of treatment is recommended if such symptoms develop.

Dyskinesia

Inbrija may cause dyskinesia. Adjustment of levodopa therapy or other medicinal products used for the treatment of Parkinson's disease may be considered.

Cardiovascular ischaemic events

Inbrija should be administered with caution in patients with severe cardiovascular disease. Care should be exercised when Inbrija is administered to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the initiation of treatment with Inbrija.

Peptic ulcer disease

Levodopa should be administered cautiously to patients with a history of peptic ulcer disease (because of the possibility of upper gastro-intestinal haemorrhage).

Glaucoma

Levodopa may cause increased intraocular pressure in patients with glaucoma. Patients with chronic glaucoma may be treated cautiously with levodopa 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.

Periodic skin examinations are recommended to monitor for melanoma in patients receiving Inbrija.

Laboratory monitoring

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), and bilirubin. Abnormalities in blood urea nitrogen (BUN) and positive Coombs test have also been reported.

Interference with test

Levodopa may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on levodopa/dopa-decarboxylase inhibitor 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/dopa-decarboxylase inhibitor therapy.

Orthostatic hypotension

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

Intercurrent respiratory infection

There is limited data available on the use of Inbrija during a respiratory infection. Based on individual assessments of the severity of the intercurrent respiratory infection Inbrija may be continued or discontinued until the respiratory symptoms resolve (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Non-selective Monoamine Oxidase (MAO) inhibitors

The use of non-selective MAO inhibitors with levodopa is contraindicated (see section 4.3). Any non-selective MAO inhibitors should be discontinued at least 14 days prior to initiating levodopa.

Selective Monoamine Oxidase (MAO) inhibitors

The use of selective MAO-B inhibitors (e.g. rasagiline, selegiline, and safinamide) with levodopa may be associated with orthostatic hypotension. Patients who are taking these medicinal products should be monitored closely.

Dopamine D2 receptor antagonists and isoniazid

Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the effectiveness of levodopa. Patients who are taking these medicinal products should be monitored for worsening Parkinson's symptoms (see section 4.4).

Antihypertensives

Symptomatic postural hypotension has occurred when combinations of levodopa and a dopa-decarboxylase inhibitor are added to the treatment of patients already receiving certain antihypertensives. Dose adjustment of the antihypertensive medicinal products may be required during concomitant use of Inbrija.

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 oral levodopa medicinal products, due to a delayed absorption. A dose adjustment of levodopa may be required.

COMT inhibitors

The addition of entacapone to a levodopa/dopa-decarboxylase inhibitor has been demonstrated to increase the levodopa bioavailability by 30%. A dose adjustment of levodopa may be required with concomitant use of COMT inhibitors.

Tricyclic antidepressants

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and a levodopa/dopa-decarboxylase inhibitor.

Amantadine

Concurrent administration of levodopa and amantadine may increase confusion, hallucinations, nightmares, gastro-intestinal disturbances, or other atropine-like side

effects. Psychotic reactions have been observed in patients receiving amantadine and levodopa.

Local or systemic pulmonary medicinal products

Interactions of Inbrija with local or systemic pulmonary medicinal products were not investigated because Inbrija is not recommended in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of levodopa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Inbrija is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Levodopa is excreted in human milk. There is insufficient information on the effects of levodopa in newborns/infants. Breast-feeding should be discontinued during treatment with Inbrija.

Fertility

There are no data on the effects of levodopa on human fertility. Animal studies indicated no effect on fertility (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 other forms of levodopa medicinal products, may affect some patients' ability to drive or use machines.

Patients being treated with levodopa medicinal products 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. use machines), until such recurrent episodes and somnolence have resolved (see also section 4.4).

4.8 Undesirable effects

Summary of safety profile

The most frequent adverse reactions reported in the Inbrija clinical studies were cough (15.6%), fall (8.7%), upper respiratory tract infection (5.8%), dyskinesia (5.7%) and sputum discoloured (2.8%). Serious adverse reactions of allergic oedema have been reported with levodopa medicinal products but not in clinical studies with Inbrija. A symptom complex resembling neuroleptic malignant syndrome and rhabdomyolysis may occur with levodopa/dopa-decarboxylase inhibitor medicinal products, although no cases have been identified in clinical studies with Inbrija. Gastrointestinal haemorrhage has been reported with levodopa medicinal products and was observed once in Inbrija clinical studies.

Tabulated list of adverse reactions

Adverse reactions are presented by system organ class and frequency in Table 1 below. Frequency categories are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), not known (cannot be estimated from the available data).

Table 1: Adverse reactions

	Adverse reactions with Inbrija			**Adverse reactions reported with oral levodopa**
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)				Malignant melanoma
Blood and lymphatic system disorders				Anaemia, Agranulocytosis, Thrombocytopenia, Leukopenia
Immune system disorder				Allergic oedema
Metabolism and				Decreased appetite

	Adverse reactions with Inbrija			**Adverse reactions reported with oral levodopa**
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
nutrition disorders				
Psychiatric disorders				Confusional state, Hallucination, Depression, Anxiety, Abnormal dreams, Insomnia, Psychotic disorder, Impulse-control disorder (see section 4.4), Agitation, Suicide attempt (see section 4.4), Disorientation, Dopamine dysregulation syndrome, Euphoric mood, Libido increased, Bruxism, Paranoia, Delusion
Nervous system disorders		Dyskinesia		Dystonia, On and off phenomenon, Somnolence, Dizziness, Worsening of Parkinson’s disease, Paraesthesia, Headache, Tremor, Seizure, Sudden onset of sleep (see section 4.4), Restless legs syndrome, Neuroleptic malignant syndrome (see section 4.4), Ataxia, Dysgeusia, Cognitive disorder,

	Adverse reactions with Inbrija			**Adverse reactions reported with oral levodopa**
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
				Horner's syndrome, Dementia
Eye disorders				Vision blurred, Diplopia, Mydriasis, Oculogyric crisis, Blepharospasm
Cardiac disorders				Cardiac rhythm disorders[a] (see section 4.4), Palpitations
Vascular disorders				Orthostatic hypotension (see section 4.4), Hypertension, Syncope, Thrombophlebitis, Hot flush
Respiratory, thoracic and mediastinal disorders	Cough	Upper respiratory tract infection, Sputum discoloured, Nasal discharge discolouration, Throat irritation	Sensation of choking	Dyspnoea, Respiration abnormal, Dysphonia, Hiccups
Gastrointestinal disorders		Nausea, Vomiting		Abdominal pain, Constipation, Diarrhoea, Dry mouth, Gastrointestinal haemorrhage, Peptic ulcer (see section 4.4), Dysphagia, Dyspepsia, Glossodynia, Flatulence, Saliva discolouration, Salivary hypersecretion
Skin and subcutaneous tissue disorders				Angioedema, Hyperhidrosis, Rash, Pruritus,

	Adverse reactions with Inbrija			**Adverse reactions reported with oral levodopa**
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
				Henoch-Schonlein purpura, Urticaria, Alopecia, Sweat discolouration
Musculoskeletal and connective tissue disorders				Muscle spasms, Trismus
Renal and urinary disorders				Urinary retention, Chromaturia, Urinary incontinence
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions				Oedema peripheral, Asthenia, Fatigue, Malaise, Gait disturbance, Chest pain
Investigations				Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood lactate dehydrogenase increased, Blood bilirubin increased, Blood glucose increased, Blood creatinine increased, Blood uric acid increased, Haemoglobin decreased, Haematocrit decreased, Blood urine present, Blood urea increased, Blood alkaline phosphatase

	Adverse reactions with Inbrija			Adverse reactions reported with oral levodopa
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
				increased, Coombs test positive, White blood cells urine positive, Bacterial test positive, Weight decreased, Weight increased
Injury, poisoning and procedural complications		Fall		

[a] Cardiac rhythm disorder here is a combined term representing atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block, sick sinus syndrome, bradycardia, and tachycardia.

Description of selected adverse reactions

Sudden sleep onset

Levodopa 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).

Coughing

Most cough reported in the clinical studies with Inbrija were mild to moderate in intensity, and usually reported within the first 30 days of the treatment. Due to cough, 2% of subjects withdrew from the clinical studies with Inbrija.

Sensation of choking

In post-marketing experience, there have been reports of the sensation of choking associated with the drug powder impacting the back of the throat, immediately following administration.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The acute symptoms of levodopa overdose can be expected to arise from dopaminergic overstimulation. Using more than one dose of Inbrija (2 capsules) to treat the same OFF period may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g. hypotension, tachycardia) and more severe psychiatric problems at higher doses.

Patients should be monitored and supportive care should be provided. Patients should receive electrocardiographic monitoring for the development of arrhythmias; if needed, appropriate antiarrhythmic therapy should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, dopaminergic agents, ATC code: N04BA01

Mechanism of action

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

Clinical efficacy and safety

The effectiveness of Inbrija for the treatment of OFF episodes in patients with Parkinson’s disease given on top of background dopaminergic treatment was evaluated in a 12-week, randomised, placebo-controlled, double-blind study. Subjects had to be able to recognise OFF periods and to handle the device.

A total of 114 patients were randomised and treated with Inbrija 66 mg (two 33 mg capsules) and 112 patients received placebo. When experiencing an OFF period,

subjects could use inhaled levodopa on demand up to five times a day. Apomorphine was not allowed as background medicinal product. At baseline, patients had at least 2 hours of OFF time per day, and the levodopa/dopa-decarboxylase inhibitor medicines did not exceed 1,600 mg levodopa per day.

The primary efficacy endpoint was the mean change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) part III score 30 minutes post dose at week 12. The UPDRS part III is designed to assess the severity of the cardinal motor findings (e.g. tremor, rigidity, bradykinesia, postural instability) in patients with Parkinson's disease. This endpoint was assessed in a clinical setting, i.e. patients had to take their regular morning oral levodopa/dopa-decarboxylase inhibitor dose and then visit the clinic 2-5 hours post dose. If an OFF period emerged subjects received placebo or inhaled levodopa. UPDRS-III was assessed before and 30 minutes post dose administration. Reduction in mean daily OFF time and improvement on the Patient Global Impression of Change (PGI-C) scale, a patient reported outcome of the overall improvement and satisfaction with Inbrija treatment, and Responders ON were the main secondary endpoints. Results are presented in Table 2.

Table 2: Baseline features and results of the efficacy endpoints

Parameters	Placebo n = 112	Inbrija 66 mg n = 114
Subject features		
Age	63 years	64 years
Duration PD	97 months	96 months
Baseline Levodopa dose	841 mg	819 mg
UPDRS-III score during OFF period	n = 95[a]	n = 94[a]
Pre-dose score	32.1	29.0
Change at 30 min	-5.91	-9.83
Diff. (95% CI)	-	-3.92 (-6.84; -1.00)
p-value	-	0.009
Responders ON[b]	n = 97[a]	n = 97[a]
% (n)	36.1% (35)	57.7% (56)
Diff.	-	21.6%
p-value	-	0.003
PGI-C	n = 97[a]	n = 98[a]
Much improved % (n)	7.2% (7)	11.2% (11)
Improved % (n)	7.2% (7)	26.5% (26)
Little improved % (n)	32.0% (31)	33.7% (33)
Not improved % (n)	53.6% (52)	28.6% (28)
p-value	-	< 0.001[c]
Daily OFF-time (h)	n = 97[a]	n = 95[a]
Baseline mean (SD)	5.59 (2.25)	5.35 (2.26)
LS mean change	-0.48	-0.47
Mean diff. (95% CI)		-0.01 (-0.55; 0.56)
p-value		0.975
Daily doses (median)	2 doses	2 doses

[a] Observed cases.
[b] A responder was defined as a subject that changed from OFF to ON within 60 minutes post dose and who remained ON at 60 minutes post dose.
[c] p-value for PGI-C is nominal.

Pulmonary safety

In a subpopulation of the 12-week study, serial spirometry measurements were performed at 15, 30 and 60 minutes following the first dose of Inbrija 66 mg or placebo. No notable differences between placebo and Inbrija were observed in forced expiratory volume in 1 second (FEV_1) following the first dose.

The effect of Inbrija on pulmonary function was also evaluated in patients with Parkinson's disease treated with an oral levodopa/dopa-decarboxylase inhibitor in a 12-month, randomised, controlled, open-labeled study. A total of 271 patients were treated with Inbrija 66 mg (two 33 mg capsules), and 127 patients in an observational control group were observed on their regular oral medication regimen for the treatment of Parkinson's disease. Pulmonary function was assessed by spirometry and

carbon monoxide diffusing capacity (DL_{CO}) every 3 months in both groups. After 12 months, the average reduction in FEV_1 from baseline was the same in both groups (-0.1 L). The change from baseline for DL_{CO} was compared between the Inbrija treatment group and the observational cohort; at the end of 12 months, there was no significant difference in the change from baseline between Inbrija group and the observational cohort in DL_{CO}.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Inbrija 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

The pharmacokinetics of Inbrija 66 mg (2 x 33 mg capsules) and carbidopa/levodopa 25 mg/100 mg immediate release tablets was evaluated in 24 healthy volunteers in a fasted state receiving a total of 50 mg carbidopa every 8 hours.

The median time to maximal plasma concentration of levodopa was 30 minutes after a dose of Inbrija 66 mg (2 x 33 mg capsules) compared to 45 minutes after a dose of carbidopa/levodopa 25 mg/100 mg immediate release tablets. The dose-normalised relative bioavailability of a single 66 mg emitted dose of Inbrija was 88.0% (90% CI: 80.3, 96.4) when compared to a single oral carbidopa/levodopa 25 mg/100 mg dose.

The mean maximal plasma concentration at 10 minutes (C_{10min}) and at peak concentration (C_{max}) of levodopa following administration of Inbrija 66 mg (2 x 33 mg capsules) was 418 ng/mL and 696 ng/mL, respectively, with exposure over 4 hours ($AUC_{0\text{-}4\,h}$) of 1,280 ng•h/mL.

Distribution

Apparent volume of distribution (V_z/F) was 168 L for Inbrija 66 mg (2 x 33 mg capsules).

Biotransformation

Levodopa is extensively metabolised to various metabolites. The two major metabolic pathways are decarboxylation by L-aromatic amino acid decarboxylase and O-methylation by catechol-O-methyltransferase (COMT).

The pharmacokinetics of the major levodopa metabolites 3-O-methyldopa (3-OMD), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were studied following administration of a single inhaled dose of Inbrija and a single oral carbidopa/levodopa 25 mg/100 mg immediate release tablet. The metabolite profile following Inbrija inhalation was not substantially different than that observed following oral carbidopa/levodopa administration. The peak metabolite concentrations and total exposure achieved after Inbrija administration did not exceed those observed following an oral carbidopa/levodopa dose.

The impact of the amount of circulating dopa-decarboxylase at the end of an oral carbidopa/levodopa dosing interval on the efficacy of Inbrija was not studied.

Elimination

In the presence of carbidopa, the apparent terminal elimination half-life ($t_{1/2}$) of levodopa following a single administration of Inbrija 66 mg (2 x 33 mg capsules) was 2.3 hours and comparable to that following an oral dose of carbidopa/levodopa 25 mg/100 mg immediate release tablets of 1.9 hours.

Linearity/non-linearity

Inbrija shows dose proportional pharmacokinetics of levodopa from 13 mg to 122 mg.

Renal impairment

Inbrija has not specifically been studied in patients with renal impairment. It is recommended to administer this medicinal product cautiously to patients with severe renal disease (see section 4.2).

Hepatic impairment

Inbrija has not specifically been studied in patients with hepatic impairment. It is recommended to administer this medicinal product cautiously to patients with severe hepatic impairment (see section 4.2).

Gender

A clinical study was performed with Inbrija 66 mg (2 x 33 mg capsules) in 24 healthy subjects (13 men and 11 women). After administration of Inbrija the C_{max} and $AUC_{0-24\ h}$ for women were 42.2% higher and 48.8% higher than for men, respectively. After correcting the parameters for body weight, the gender difference after each treatment was no longer significant: the body-weight adjusted C_{max} and $AUC_{0-24\ h}$ after a dose of Inbrija in women were 9.7% and 15.1% higher than men. Most of the gender difference is accounted for by differences in body weight. No dose adjustment is required based on gender.

Smoking

A clinical study was performed with Inbrija 66 mg (2 x 33 mg capsules) administered to 56 healthy subjects (31 non-smokers and 25 smokers). After administration of Inbrija the C_{max} and $AUC_{0-24\ h}$ was 11% to 12% higher for smokers than for non-smokers. No dose adjustment is required based on smoking status.

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 toxicity

Levodopa has 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Colfosceril palmitate (DPPC)

Sodium chloride

Capsule shell

Hypromellose
Titanium dioxide (E 171)
Carrageenan
Potassium chloride
Carnauba wax
Maize starch

Ink

Shellac
Black iron oxide (E 172)
Propylene glycol
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light and moisture and remove immediately before use.

6.5 Nature and contents of container

The hard capsules are supplied in Aluminium / PVC / Aluminium peel-off blisters. Each perforated unit-dose blister strip contains 4 hard capsules.

The Inbrija inhaler is made of polybutylene terephthalate (PBT), polycarbonate (PC) and polypropylene (PP). Puncturing tines and springs are made from stainless steel.

Carton containing 16 hard capsules (4 blister strips) and one inhaler.

Carton containing 32 hard capsules (8 blister strips) and one inhaler.

Carton containing 60 hard capsules (15 blister strips) and one inhaler.

Carton containing 92 hard capsules (23 blister strips) and one inhaler.

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

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Ireland

Tel: +353 (0)1 231 4609

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 51169/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

13/10/2025