ANNEX I

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 nutrition disorders				Decreased appetite
Psychiatric disorders				Confusional state, Hallucination, Depression, Anxiety, Abnormal dreams, Insomnia, Psychotic disorder, Impulse-control disorder (see section 4.4),

	Adverse reactions with Inbrija			**Adverse reactions reported with oral levodopa**
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
				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, 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	Cough	Upper respiratory tract infection,	Sensation of choking	Dyspnoea, Respiration abnormal, Dysphonia,

	Adverse reactions with Inbrija			**Adverse reactions reported with oral levodopa**
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
mediastinal disorders		Sputum discoloured, Nasal discharge discolouration, Throat irritation		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, 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,

	Adverse reactions with Inbrija			Adverse reactions reported with oral levodopa
System Organ Class	**Very common**	**Common**	**Not known**	**Not known**
				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 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 national reporting system listed in Appendix V.

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

Acorda Therapeutics Ireland Limited
10 Earlsfort Terrace
Dublin 2, D02 T380
Ireland
Tel: +353 (0)1 231 4609

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1390/001
EU/1/19/1390/002
EU/1/19/1390/003
EU/1/19/1390/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal: 13 June 2024

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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

ADOH B.V.
Godfried Bomansstraat 31
6543 JA Nijmegen
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Inbrija 33 mg inhalation powder, hard capsules
levodopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 42 mg levodopa.
Each delivered dose contains 33 mg levodopa.

3. LIST OF EXCIPIENTS

Contains colfosceril palmitate (DPPC), sodium chloride, hypromellose, titanium dioxide (E 171), carrageenan, potassium chloride, carnauba wax, maize starch, shellac, black iron oxide (E 172), propylene glycol, potassium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

16 hard capsules + 1 inhaler
32 hard capsules + 1 inhaler
60 hard capsules + 1 inhaler
92 hard capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For inhalation use only. Do not swallow Inbrija capsules.
For use only with the inhaler provided in the pack.

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

9. SPECIAL STORAGE CONDITIONS

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

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

Acorda Therapeutics Ireland Limited
10 Earlsfort Terrace
Dublin 2, D02 T380
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1390/001 60 hard capsules
EU/1/19/1390/002 92 hard capsules
EU/1/19/1390/003 16 hard capsules
EU/1/19/1390/004 32 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inbrija

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Inbrija 33 mg inhalation powder, hard capsules
levodopa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Acorda Therapeutics Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not swallow capsules. Inhalation only.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Inbrija 33 mg inhalation powder, hard capsules
levodopa

Read all of this leaflet carefully before you start using 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 Inbrija is and what it is used for

The active substance in Inbrija is levodopa. Inbrija is a medicine used by inhalation for treating the worsening of your symptoms during the “off periods” of Parkinson’s disease.

Parkinson’s disease affects your movement and it is treated with a medicine that you take regularly. During off periods your usual medicine does not control the condition well enough and movement is likely to be more difficult.

You should continue taking your main medicine for Parkinson’s disease and use Inbrija to control worsening of symptoms (such as inability to move) during off periods.

2. What you need to know before you use Inbrija

Do not use Inbrija:
- if you are **allergic to levodopa** or any of the other ingredients of this medicine (listed in section 6).
- if you get blurred vision, red eyes, severe eye and head pain, halos around lights, pupils of your eyes that are larger than normal size and feel sick. If you have any of these symptoms, you may have a eye condition called **narrow angle glaucoma,** which occurs suddenly: **do not** take Inbrija and **get urgent medical attention**.
- if you have a **rare tumour of the adrenal gland** called phaeochromocytoma.
- if you are taking certain **antidepressant medicines called non-selective MAO inhibitors** (e.g. isocarboxazid and phenelzine). You must stop taking these medicines at least 14 days before starting treatment with Inbrija. See also under “Other medicines and Inbrija”.
- if you have previously suffered from **neuroleptic malignant syndrome,** a life-threatening reaction to certain medicines used to treat severe mental disorders or if you have suffered from **non-traumatic rhabdomyolysis**, a rare muscle disorder in which damaged muscle breaks down rapidly.

Warnings and precautions
Get urgent medical help if you have tremors, agitation, confusion, fever, rapid pulse, or dizziness

and fainting upon standing up, or you notice that your muscles get very rigid or jerk violently. These may be symptoms of “withdrawal-emergent hyperpyrexia”. For more information see section 4.

Talk to your doctor or pharmacist before using Inbrija if you have, or have ever had, or you develop:
- asthma, breathing difficulties like chronic obstructive pulmonary disease (COPD) or other long-term lung diseases or breathing problems;
- any form of severe mental disorder like psychosis;
- a heart attack, or heart beat problems. Your doctor will monitor you closely during start of treatment;
- an ulcer in your stomach or intestines;
- an eye condition called glaucoma, because the pressure in your eyes may need to be monitored;
- severe problems with your kidneys;
- severe problems with your liver.

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

Talk to your doctor or pharmacist if you develop any of the symptoms below **whilst using** Inbrija:
- **sudden sleep attacks** or sometimes feeling very sleepy;
- **changes in or worsening of your mental state**, which may be severe such as psychotic and suicidal behaviour;
- **hallucinations,** along with being confused, unable to sleep and excessive dreaming. Abnormal thinking including anxiety, depression, being agitated, being paranoid, delusional, or disorientated, aggressive behaviour and delirious;
- worsening of any **breathing symptoms** or having a **respiratory infection**;
- **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.**
- new or increased **abnormal body movements** (dyskinesia);
- **feeling dizzy when getting up** (low blood pressure);
- **melanoma** (a type of skin cancer) or suspicious skin growths or marks.

If you need to have surgery, tell your doctor that you are using Inbrija.

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

Children and adolescents
The use of Inbrija is not recommended in patients under 18 years of age.

Other medicines and Inbrija
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 Inbrija works.

Do not use Inbrija if you have taken medicines called non-selective MAO inhibitors for treating depression in the last 14 days. These medicines include isocarboxazid and phenelzine. If this applies to you, do not take Inbrija and ask your doctor or pharmacist for advice.

Tell your doctor or pharmacist if you are taking:
- medicines for your Parkinson’s disease called selective MAO inhibitors such as rasagiline, selegiline and safinamide, COMT inhibitors such as entacapone, tolcapone and opicapone, or anticholinergics such as orphenadrine and trihexyphenidyl;

- medicines for mental conditions including schizophrenia, such as benperidol, haloperidol, risperidone, chlorpromazine, fluphenazine decanoate, phenotiazine, butyrophenone, or trifluoperazine;
- metoclopramide to treat nausea;
- isoniazid, an antibiotic to treat tuberculosis;
- medicines for high blood pressure, as the dose may need to be adjusted;
- medicines for depression called tricyclic antidepressants such as clomipramin, desipramin, or doxepin;
- amantadine to treat flu or your Parkinson's disease.

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

Treatment with Inbrija is not recommended during pregnancy and in women of childbearing age who do not use contraception.

Women should not breast-feed during treatment with Inbrija.

Driving and using machines
Inbrija can cause **excessive drowsiness, dizziness** and **sudden sleep attacks**. If this happens to you, **do not** drive or use tools or machines. You must be sure that you do not get sudden sleep attacks, dizziness and drowsiness before you drive again or use machines. You could put yourself or others at risk of serious injury or death.

3. How to use Inbrija

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

Before starting Inbrija, you must be taking regular treatment for Parkinson's disease combining a so-called dopa-decarboxylase inhibitor with levodopa.

The recommended dose of Inbrija is **2 capsules** to treat each off period. Do not use more than 2 capsules for each off period. You can use 2 capsules up to five times a day.

The maximum dose of Inbrija is 10 capsules per day.

Important information before you use Inbrija:
- **Inbrija capsules must not be swallowed.**
- This medicine is for **use by inhalation only**.
- The capsules must only be removed from the blister pack immediately before use.
- Two capsules of medicine should be inhaled to get the full dose.
- The medicine must be used only with the Inbrija inhaler device.
- When you open a new carton, always use the new inhaler supplied.
- Your doctor or pharmacist will show you how to use your medicine correctly.

Please see the "**Instructions for use**" at the end of this leaflet on how to use your medicine with the provided inhaler.

If you use more Inbrija than you should
If you use more Inbrija than you should (or someone accidentally swallows Inbrija) **get medical help immediately.** You may feel confused or agitated, and your heart rate may be slower or faster than normal.

If you forget to use Inbrija
Use Inbrija only during an off period. If the off period has passed, do not use Inbrija until the next off period.

If you stop using Inbrija
Do not stop using Inbrija without checking with your doctor.

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.

Get urgent medical help if you have an allergic oedema with symptoms including hives (nettle rash), itching, rash, swelling of your face, lips, tongue, or throat. This may cause difficulties in breathing or swallowing.

Get urgent medical help if 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).

Get urgent medical help if you have bleeding in your stomach or intestines which may be seen as blood in your faeces or darkened faeces.

The following side effects may happen with this medicine:
Very common (may affect more than 1 in 10 people):
- cough

Common (may affect up to 1 in 10 people):
- new or increased abnormal body movements (dyskinesia);
- infections of nose, sinuses, throat or lungs;
- change in colour of your mucus;
- discoloured (i.e. not clear) nasal mucus;
- irritation in throat or itchy throat;
- feeling sick (nausea); vomiting;
- being prone to falls.

<u>Other side effects you may experience of which the frequency is not known include:</u>

- sensation of choking associated with the drug powder impacting the back of the throat, immediately after use
- skin cancer;
- lack of red blood cells so you are pale and feel tired; being more prone to infections because of a lack of white blood cells; lack of blood platelets which can lead to bruising and a tendency to bleed;
- decreased appetite;
- confusion; hallucinations; depression; anxiety; bad dreams; unable to sleep; abnormal thinking and perceptions, losing touch with reality; feeling agitated; suicidal; being disorientated; exaggerated feeling of happiness; increased sex drive; grinding of teeth; feeling paranoid and delusional;
- movement disorder in which a person's muscles contract uncontrollably; sudden, sometimes unpredictable changes in symptoms, due to the return of Parkinson’s disease symptoms; sleepiness; dizziness; worsening of Parkinson’s disease; pins and needles; headache; tremors; seizure; sudden onset of sleep; restless legs syndrome; ataxia (disorder affecting co-ordination,

balance and speech); distorted sense of taste; mental health disorders that affecting learning, memory, perception, and problem solving; Horner's syndrome (an eye disorder); dementia;
- blurred vision; double vision; widening pupil; prolonged rolling eyes upwards; involuntary tight closure of the eyelids;
- heart problems, a noticeably rapid, strong, or irregular heartbeat;
- low blood pressure soon after standing up; high blood pressure; fainting; blood clot in a vein; hot flushes;
- shortness of breath; difficulty in breathing; difficulty in speaking; hiccups;
- stomach pains; constipation; diarrhoea; dry mouth; stomach and intestinal bleeding; stomach ulcer; difficulty in swallowing; indigestion; burning sensation in the mouth; passing wind; change in colour of saliva; more saliva than normal;
- swelling of face, lips, tongue, limbs and genitals; excessive sweating; rash; severe itching of the skin; condition called Henoch-Schoenlein purpura, the symptoms of which include a purple spotted skin rash; allergic reaction causing a rash of round, red welts on the skin that itch intensely; hair loss; discoloured sweat;
- muscle spasms; lockjaw;
- difficulty in emptying the bladder; abnormal urine colour; loss of bladder control;
- painful, abnormally long-lasting erection;
- swelling of lower legs or hands; feeling weak and having no energy; feeling tired; lack of energy; difficulty in walking; chest pain;
- abnormal blood investigation results; weight loss; weight gain.

<u>You may experience the following side effects:</u>

- 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;
  - altersed 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.

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 Inbrija

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

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

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

Do not use any capsule that looks crushed, damaged or wet.

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 Inbrija contains
- The active substance is levodopa. Each hard capsule contains 42 mg levodopa. The dose that leaves the mouthpiece of the inhaler (delivered dose) is 33 mg of levodopa.
- The other ingredients comprising the powder and capsule are colfosceril palmitate (DPPC), sodium chloride, hypromellose, titanium dioxide (E 171), carrageenan, potassium chloride, carnauba wax, maize starch, shellac, black iron oxide (E 172), propylene glycol and potassium hydroxide.

What Inbrija looks like and contents of the pack
Inbrija inhalation powder, hard capsules consist of a white powder for inhalation filled into white opaque hard capsules with “A42” printed in black on the cap of the caspule and two black bands printed on the body of the capsule.

In this pack, you will find an inhaler together with peel-off blisters containing 4 hard capsules each.

The pack sizes are
- a carton containing 16 hard capsules (4 blister strips) and one inhaler
- a carton containing 32 hard capsules (8 blister strips) and one inhaler
- a carton containing 60 hard capsules (15 blister strips) and one inhaler
- a carton containing 92 hard capsules (23 blister strips) and one inhaler

Not all pack sizes may be marketed.

Marketing Authorisation Holder
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Manufacturer
ADOH B.V.
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Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

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

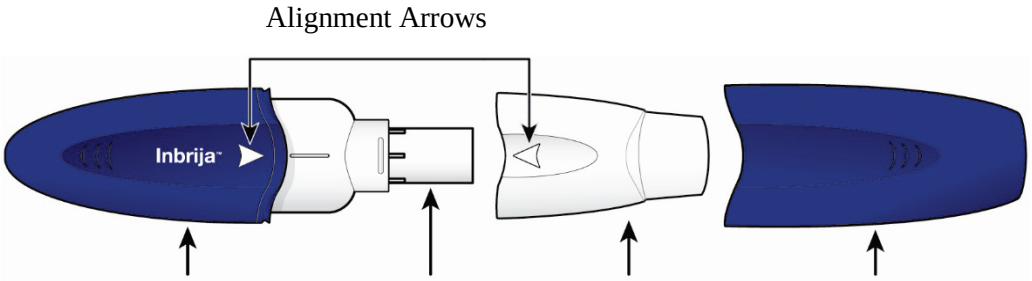
Instructions for use:

Read these instructions before you start using Inbrija.

Overview

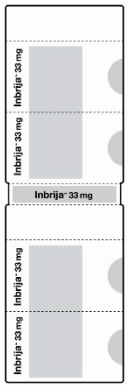
- Make sure your hands are clean and dry when using the inhaler and capsules.
- Only remove the capsules from the blister immediately before use.
- A complete dose is 2 capsules used one after the other.
- Load 1 capsule into the Inbrija inhaler, close your lips firmly around the mouthpiece, then breathe in (inhale) and hold that breath for 5 seconds. You should hear the capsule "whirl". Then, remove the used capsule and load a second capsule into the inhaler. Close your lips firmly around the mouthpiece and breathe in, again holding your breath for 5 seconds.
- You should inhale the contents of the second capsule within 10 minutes of the first one.
- Do not load 2 capsules at the same time.
- Dispose of all used capsules immediately after use.
- Dispose of the inhaler after you are finished all of the capsules in the carton.

Parts of your Inbrija inhaler



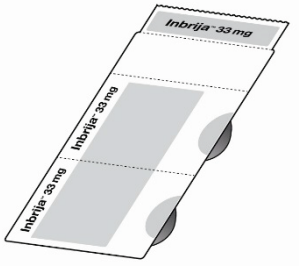
Capsules

Each carton includes blisters of 4 capsules.

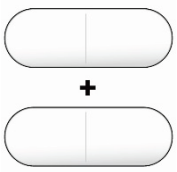


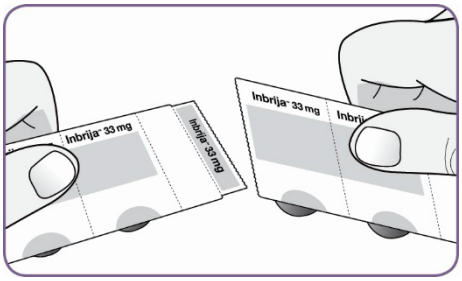
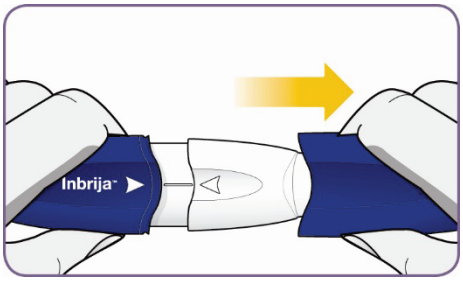
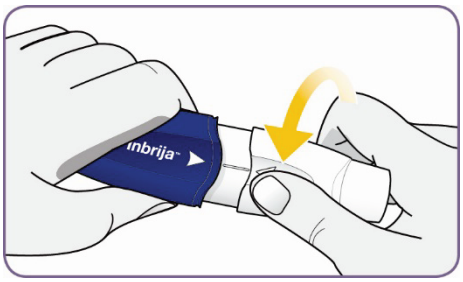
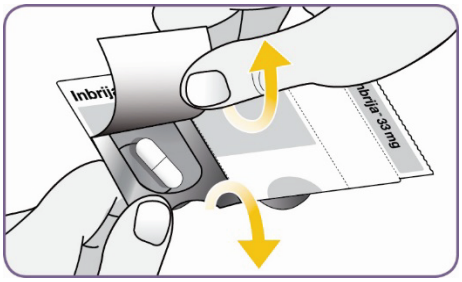
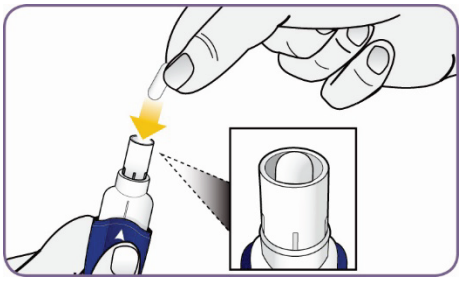
Prepare and use a total of 2 capsules.

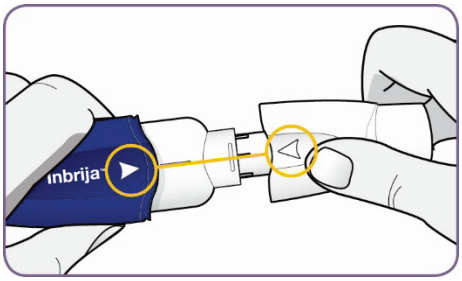
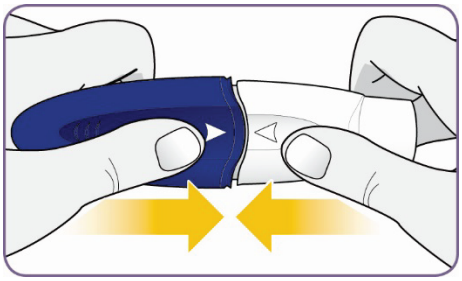
Use one capsule at a time.

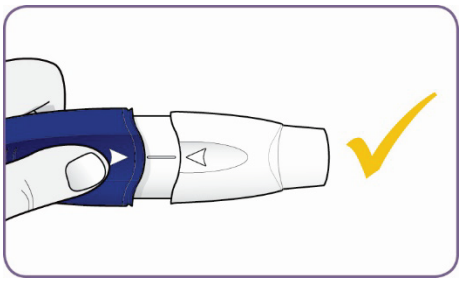


Full dose = 2 capsules.

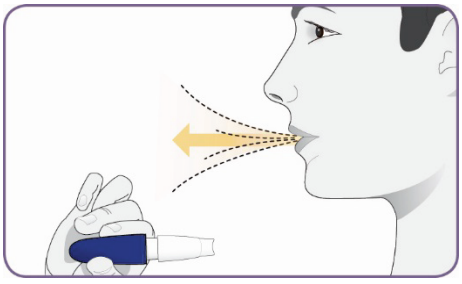


Prepare your dose	
Step 1: Gather supplies 	Find a clean and dry surface. Make sure your hands are clean and dry. Get inhaler and strip of capsules. Tear off package of 2 capsules. **A full dose is 2 capsules.**
Step 2: Remove blue cap from inhaler 	Pull the cap straight off. Place the cap to the side. You will need it later to store the inhaler.
Step 3: Twist and pull off white mouthpiece 	Twist and pull off the mouthpiece to separate it from the handle. Place the mouthpiece and inhaler on a clean and dry surface.
Step 4: Remove 1 capsule from package 	Carefully peel back the foil and take out 1 capsule. Only remove 1 capsule at a time, and just before use. Do not use any capsule that looks crushed, damaged or wet. Dispose of it and get a new capsule.
Step 5: Load capsule 	Hold the inhaler upright using the handle. Drop 1 capsule into the opening of the capsule chamber. Do not load 2 capsules at the same time.

<table>
<tr><td colspan="2">Step 6: Attach white mouthpiece</td></tr>
<tr><td>Align arrows on mouthpiece and handle
  </td><td>Line up the white arrows on the handle and mouthpiece.</td></tr>
<tr><td>Compress mouthpiece only once
  </td><td>Firmly push the mouthpiece and handle together until you hear a click. This punctures the capsule.

Do not push the handle and mouthpiece together more than once.</td></tr>
<tr><td>Release mouthpiece
  </td><td>Release the mouthpiece. The mouthpiece will spring back and stay attached.</td></tr>
<tr><td colspan="2">Your inhaler is now ready to use.

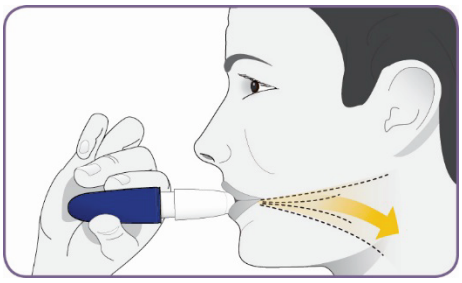
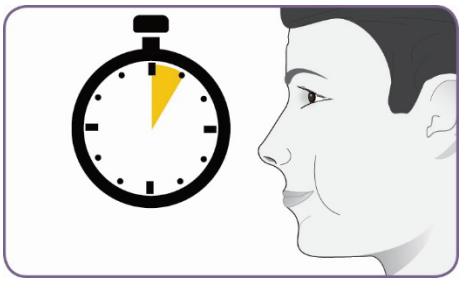
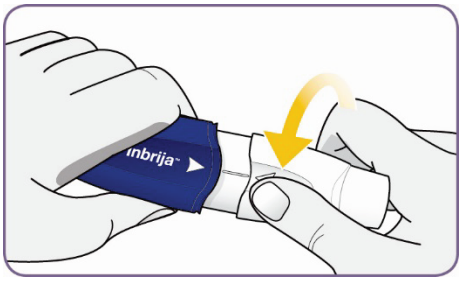
Do not push the handle and mouthpiece together more than once. This may damage the capsule, and you may not get your full dose. If this happens start again at Step 4 using a new capsule.

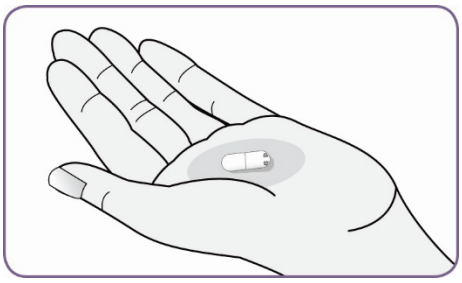
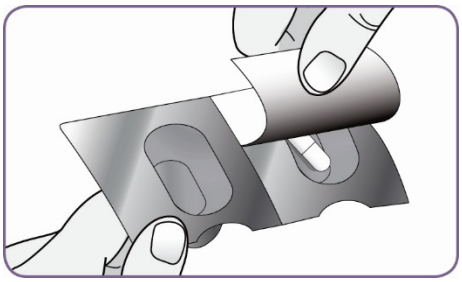
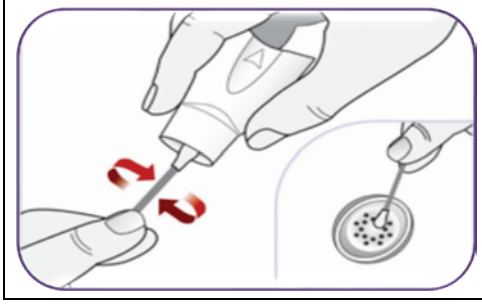
Make sure the mouthpiece is securely attached and will not fall off before moving to Step 7.</td></tr>
<tr><td colspan="2">Take your dose</td></tr>
<tr><td>Step 7: Hold inhaler away and breathe out
  </td><td>Stand or sit with your head and chest upright.

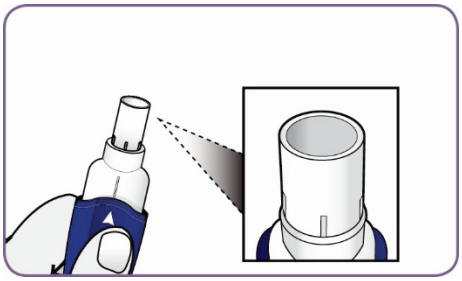
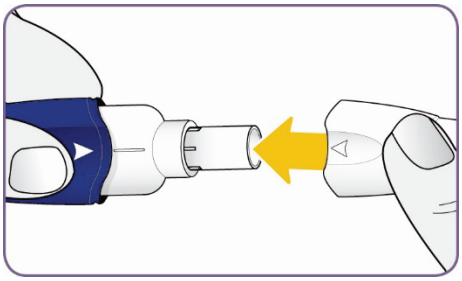
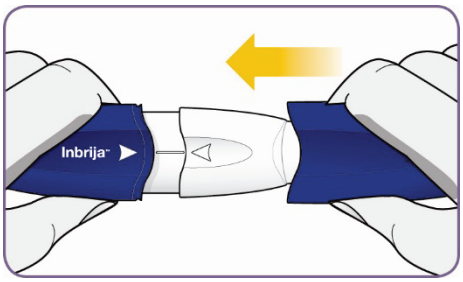
Hold the inhaler level and away from your mouth.

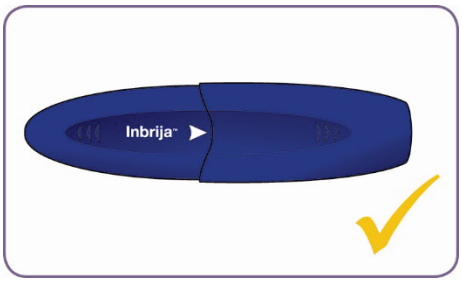
Breathe out completely.

Do not breathe into mouthpiece.</td></tr>
</table>

Step 8: Breathe in deeply to inhale powder 	While keeping the inhaler level, close your lips firmly around the mouthpiece. **Take in a deep, comfortable breath until your lungs feel full. This normally takes several seconds.** As you breathe in, you will hear and feel the capsule “whirl” (spin). The whirl means the inhaler is working and you are getting your medicine. If you cough or stop your dose, start again from the beginning of Step 7 using the same capsule. **Important: If you did not hear or feel the capsule “whirl” while inhaling you may need to take a deeper, longer breath or may need to clean the mouthpiece (Do not rinse the mouthpiece or get the inhaler wet). Refer to Step 13 – Clean Mouthpiece. Start again from the beginning of Step 7 using the same capsule.**
Step 9: Hold breath for 5 seconds, then breathe out 	Take the inhaler out of your mouth and hold your breath for 5 seconds. Then breathe out.
Step 10: Remove capsule from inhaler	
Twist and pull off the mouthpiece 	Twist and pull off the mouthpiece.

Remove used capsule 	Take out the used capsule.
Step 11: Dose with 2nd capsule 	Repeat Steps 4 to 10 with the second capsule to finish the full dose. **You should inhale the contents of the second capsule within 10 minutes of the first one.**
Dispose and store	
Step 12: Dispose of used capsules 	Dispose of used capsules in accordance with local requirements.
Step 13: Clean Mouthpiece It is normal for some powder to remain in or on the inhaler. To avoid powder buildup, clean the powder off of the mouthpiece holes using a circular motion with a new dry cotton swab as needed.	
Clean holes from the top end of mouthpiece 	Clean the holes from the top end of the mouthpiece.

Clean holes from bottom end of mouthpiece 	Clean the holes from the bottom end of the mouthpiece.
You can also use a dry tissue to wipe the outside of the mouthpiece, as needed. **Do not clean any other parts of the inhaler.** **Do not rinse the mouthpiece or get the inhaler wet.**	
Step 14: Store inhaler	
Make sure there are no capsules in the inhaler 	Make sure there are no capsules in the inhaler before you store it.
Attach mouthpiece 	Attach the mouthpiece to the handle by pushing until you hear a click.
Attach cap 	Attach the cap over the mouthpiece.

Ready for storage 	Your inhaler is now ready to store.

Cleaning the inhaler

- It is normal for some powder to remain in or on the inhaler.
- To avoid powder buildup, clean the powder off of the mouthpiece holes using a circular motion with a new dry cotton swab as needed.
- You can also use a dry tissue to wipe the inside or outside of the inhaler mouthpiece.
- **Do not clean any other parts of the inhaler. Do not rinse the mouthpiece or get the inhaler wet.**