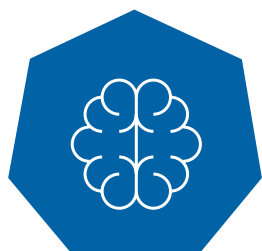


Managing OFF Episodes in Parkinson's Disease

Parkinson's disease (PD) affects an estimated 11.7 million people worldwide, with a range of motor symptoms including tremors, muscle stiffness, and slow movements, as well as non-motor symptoms such as trouble sleeping, speech problems, and depression.^{1,2} Despite the use of standard medications, many patients experience "OFF" episodes where their treatment begins to wear off and symptoms return or worsen. These often unpredictable episodes can significantly impact daily activities and quality of life.² Understanding these episodes and having effective treatment options is key to delivering better outcomes for more patients.



PD treatment

- Whilst PD has no single known cause, symptoms are caused by a lack of dopamine, a neurotransmitter that regulates movement, in the brain
 - Treatments therefore focus on replacing, mimicking, or enhancing dopamine activity in the brain.
- Levodopa is most often used to manage motor symptoms as it converts into dopamine once it reaches the brain.
 - It is used in combination with carbidopa, which prevents levodopa from breaking down before it reaches the brain, reducing the nausea caused by levodopa alone.

Why do OFF episodes occur?

- OFF episodes occur when dopamine levels in the brain fall below a certain threshold.
 - As PD progresses, the brain's capacity to produce and store dopamine continues to decline. This causes medications that mimic dopamine to lose their effectiveness more rapidly or fail to work entirely during certain periods.³
 - PD patients also often have difficulties reliably resorbing oral medicines stemming from dysphagia (swallowing problems) and gastric dysfunction, including delayed gastric emptying (gastroparesis), competing transporters in the small intestine and constipation.⁴
- The symptoms experienced during OFF episodes commonly include increased stiffness and slowness, worsening or returning tremors, freezing episodes, and muscle contractions. Other non-motor symptoms may occur or intensify, including anxiety, depression, fatigue, cognitive difficulties, and pain.⁵
- Various types of OFF episodes can occur, including dose-waning episodes – such as early-morning episodes before the first daily dose takes effect or middle-of-the-night episodes when evening medication wears off – as well as unexpected episodes unrelated to dosing schedules, episodes following large or protein-rich meals, delayed onset episodes due to digestive issues, and episodes due to complete dose failures.



As PD progresses, the brain's capacity to produce and store dopamine continues to decline. This causes medications that mimic dopamine to lose their effectiveness more rapidly or fail to work entirely during certain periods.³

INBRIJA® for the treatment of OFF Episodes



INBRIJA® (levodopa) is Merz Therapeutics' inhaled prescription levodopa medication for intermittent treatment of episodic motor fluctuations (OFF episodes) in adults with PD who are treated with (oral) levodopa/dopa-decarboxylase inhibitor medicine.⁶



- **INBRIJA** received U.S. Food and Drug Administration (FDA) approval in 2018 and European Medicines Agency (EMA) approval in 2019.
- **INBRIJA** uses proprietary ARCUS® technology to provide rapid symptom relief when OFF episodes occur, designed specifically as an on-demand therapy to complement existing levodopa/dopa-decarboxylase inhibitor treatments.



Once inhaled, levodopa is converted into dopamine within the brain, supporting the restoration of dopamine levels.



- The inhalation route bypasses the digestive system, providing rapid and consistent absorption.
- It has a large-capacity capsule and breath-actuated inhaler and can be administered on the go, enabling patients to self-manage their symptoms when OFF episodes occur.



- **INBRIJA** does not replace regular levodopa/dopa-decarboxylase inhibitor medicine.
- The most common side effects of **INBRIJA** are cough, dyskinesia, upper respiratory tract infection, sputum and nasal discharge discoloration, throat irritation, nausea, vomiting and fall.⁶

Mandatory Safety Information

Inbrija 33 mg inhalation powder, hard capsules.

Active substance: Levodopa. **Prescription only!**

Qualitative and quantitative composition:

Active substance: Each hard capsule contains 42 mg levodopa. Each delivered dose contains 33 mg levodopa. **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.

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.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, Narrow-angle glaucoma, Pheochromocytoma, Co-administration with non-selective monoamine oxidase (MAO) inhibitors, a previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

Undesirable effects: *Very common (m1/10):* Cough.

Common (m1/100 bis <1/10): Dyskinesia, Upper respiratory tract infection, Sputum discoloured, Nasal discharge discolouration, Throat irritation, Nausea, Vomiting, Fall.

Reported with oral levodopa: *not known:* Malignant melanoma, Anaemia, Agranulocytosis, Thrombocytopenia, Leukopenia, Allergic oedema, Decreased appetite, Confusional state, Hallucination, Depression, Anxiety, Abnormal dreams, Insomnia, Psychotic disorder, Impulse-control disorder, Agitation, Suicide attempt, Disorientation, Dopamine dysregulation syndrome, Euphoric mood, Libido increased, Bruxism, Paranoia, Delusion, Dystonia, On and off phenomenon, Somnolence, Dizziness, Worsening of Parkinson's disease, Paraesthesia, Headache, Tremor, Seizure, Sudden onset of sleep, Restless legs syndrome, Neuroleptic malignant syndrome, Ataxia, Dysgeusia, Cognitive disorder, Horner's syndrome, Dementia, Vision blurred, Diplopia, Mydriasis, Oculogyric crisis, Blepharospasm, Cardiac rhythm disorders, Palpitations, Orthostatic hypotension, Hypertension, Syncope, Thrombophlebitis, Hot flush, Dyspnoea, Respiration abnormal, Dysphonia, Hiccups, Abdominal pain, Constipation, Diarrhoea, Dry mouth,

Gastrointestinal haemorrhage, Peptic ulcer, Dysphagia, Dyspepsia, Glossodynia, Flatulence, Saliva discolouration, Salivary hypersecretion, Angioedema, Hyperhidrosis, Rash, Pruritus, Hensch-Schonlein purpura, Urticaria, Alopecia, Sweat discolouration, Muscle spasms, Trismus, Urinary retention, Chromaturia, Urinary incontinence, Priapism, Oedema peripheral, Asthenia, Fatigue, Malaise, Gait disturbance, Chest pain, 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 increased, Coombs test positive, White blood cells urine positive, Bacterial test positive, Weight decreased, Weight increased.

Date of revision: November 2025.

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Further information is provided in the Summary of Product Characteristics and the Package Leaflet.

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