PDL DRUG REVIEW

Proprietary Name: Inbrija®
Common Name: levodopa
PDL Category: Anti-Parkinsonian Drugs

Comparable Products	Preferred Drug List Status
Apokyn	Preferred

Summary

Pharmacology/Usage: Levodopa, the active ingredient of Inbrija®, is the metabolic precursor of dopamine. It crosses the blood-brain barrier and presumably is converted to dopamine in the brain. This is thought to be the mechanism where levodopa relieves symptoms of Parkinson's disease.

Indication: For the intermittent treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa.

There is no pregnancy category for this medication; however, the risk summary indicates there are no adequate data on the developmental risk associated with the use in pregnant women. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Inbrija® Capsules and the Inbrija® inhaler. The capsules contain 42mg dry powder formulation of levodopa

Recommended Dosage: Inbrija® capsules are for oral inhalation only and should be used only with the Inbrija® inhaler. Inbrija® capsules must NOT be swallowed as the intended effect will not be obtained. The capsules should be stored in their blister package and only removed immediately before use.

Use Inbrija® when symptoms of an OFF period start to return. The recommended dosage is the oral inhalation of the contents of two 42mg capsules (84mg) as needed, up to 5 times a day. The maximum dose per OFF period is 84mg, and the maximum daily dosage is 420mg. Inbrija® has been shown to be effective only in combination with carbidopa/levodopa.

Drug Interactions: The use of non-selective MAO inhibitors with Inbrija® is contraindicated. Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the efficacy of levodopa. Monitor patients for worsening Parkinson's symptoms. Last, iron salts or multivitamins containing iron salts can form chelates with levodopa and consequently reduce the bioavailability of levodopa.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Inbrija® 84mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events

included cough (13%), sputum discolored (5%), nasal discharge discoloration (2%), oropharyngeal pain (2%), nausea (2%), vomiting (3%), upper respiratory tract infection (3%), nasopharyngitis (1%), bronchitis/pneumonia (2%), dyskinesia (3%), headache (2%), fall (1%), laceration (2%), skin abrasion (2%), chest discomfort (2%), blood bilirubin increased (2%), red blood cell count decreased (2%), pain in extremity (1%), insomnia (1%), and orthostatic hypotension/blood pressure decreased (2%).

Patients treated with levodopa have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles. Before starting treatment, advise patients about the potential to develop drowsiness and ask about factors that may increase the risk of somnolence with Inbrija®, such as the concomitant use of sedating medications and the presence of sleep disorders.

A symptom complex that resembles neuroleptic malignant syndrome, with no obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy.

In placebo-controlled studies, hallucinations were reported in less than 2% of patients treated with Inbrija®. Hallucinations may be accompanied by confusion, insomnia, and excessive dreaming. Abnormal thinking and behavior may present with one or more symptoms. Due to the risk of exacerbating psychosis, patients with a major psychotic disorder should ordinarily not be treated with Inbrija®.

Patients treated with Inbrija® can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more the of medications that increase central dopaminergic tone. Consider stopping the medication if a patient develops such urges while taking Inbrija®.

Inbrija® may cause or exacerbate dyskinesias. If troublesome dyskinesias occur, consider stopping treatment and/or adjusting the patient's daily medications for the treatment of Parkinson's disease.

Due to the risk of bronchospasm, use of Inbrija® in patients with asthma, COPD, or another chronic underlying lung disease is not recommended.

Inbrija® may cause increased intraocular pressure in patients with glaucoma. It is recommended to monitor patients for increased intraocular pressure during treatment with Inbrija®.

Contraindications: In patients currently taking a non-selective MAO inhibitor (e.g. phenelzine and tranylcypromine) or who have recently (within 2 weeks) taken a non-selective MAO inhibitor.

Manufacturer: Acorda Therapeutics

Analysis: The safety and efficacy of Inbrija® for the treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa were assessed in a randomized, placebo-controlled, double-blind study (N=226) of 12 weeks in duration. At baseline, patients had at least 2 hours per day of OFF time per day, and the carbidopa/levodopa medication did not exceed 1600mg of levodopa per day. The mean Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores at screening in the ON state were 14.9 with the Inbrija® group and 16.1 for patients in the placebo group. 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. The average use of Inbrija® or placebo was about 2 doses per day.

The primary endpoint was the change in the UPDRS Part III motor score from pre-dose OFF state to 30-minutes post-dose, measured at week 12. At week 12, the reduction in UPDRS Part III motor score for Inbrija® 84mg as compared to placebo at 30-minutes post-dose were -9.8 and -5.9, respectively. The difference between groups was statistically significant in favor of Inbrija® (p=0.009). The proportion who returned to an ON state and sustained that ON through 60 minutes post-dose was 58% for Inbrija® and 36% for placebo, which was significantly different (p=0.003). The results of the primary endpoint can be seen in the table below, which was adapted from the prescribing information.

Treatment	Pre-dose (OFF) UPDRS Part III Motor Score (mean)	Post-dose UPDRS Part III Motor Score (Mean)	Mean Change 30 mins post-dose	Difference from placebo; p-value
Placebo	32.1	25.3	-5.9	
Inbrija® 84mg	29.0	19.3	-9.8	-3.92; p=0.009

Study 2 assessed the effect of Inbrija® on pulmonary function in patients with Parkinson's disease treated with oral carbidopa/levodopa in a 12-month, randomized, controlled, open-label study. Patients treated with Inbrija® 84mg (N=271) were compared with a control group (N=127) and were observed on their regular oral medication regimen for the treatment of Parkinson's disease. Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years were excluded. Pulmonary function was assessed by spirometry every 3 months in both groups. Results suggested that after 12 months, the average reduction in the forced expiratory volume in 1 sec (FEV1) from baseline was the same in both groups (-0.1L).

Place in Therapy: Inbrija® includes capsules containing 42mg of dry powder formulation of levodopa to be used with the Inbrija® inhaler. It is for oral inhalation use only and is indicated for the intermittent treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa. In a clinical trial compared with placebo, Inbrija® was found to have a significant change in the UPDRS Part III motor score. In addition, significantly more in the Inbrija® group returned to an ON state and sustained that ON state through 60 minutes post-dose as compared with placebo (NNT 5).

Inbrija® inhalation powder, like Apokyn® (apomorphine) injection, is effective in rapidly reducing the symptoms of off periods in Parkinson's patients. It is therefore recommended that Inbrija® be added to the Preferred Drug List as preferred.

PDL Placement: ☒ **Preferred**
☐ **Non-Preferred**

References

[1]Inbrija [package insert]. Ardsley, NY: Acorda Therapeutics, Inc; 2018.