Drug Monograph

Drug/Drug Class:	**Inbrija™ (levodopa) capsule for inhalation / Antiparkinsonism Agents, Dopamine Precursor**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Inbrija is available as an inhalation powder via 42 mg capsules for use with Inbrija inhaler. Distributed by: Acorda Therapeutics, Inc., Ardsley, NY 10502.
Summary of Findings:	The efficacy of Inbrija was demonstrated in one randomized, double-blind, placebo-controlled clinical trial in 114 patients with Parkinson's Disease (PD). The primary measure of efficacy was the change from predose in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III score to 30 minutes post dose after 12 weeks. The UPDRS part III is designed to assess the severity of the cardinal motor findings (tremor, rigidity, bradykinesia, postural instability) in patients with PD, with lower scores indicating better movement. At week 12, the mean difference in UPDRS motor score change from predose to 30 minute post dose was -3.92 (p=0.0088) between Inbrija vs placebo. The proportion of patients who returned to the ON state and sustained that ON through 60 minutes post-dose was 58% for the Inbrija and 36% for the placebo (p=0.003).
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

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Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1]

Parkinson's disease is a neurodegenerative disorder that affects predominately dopamine-producing neurons in a specific part of the brain called the substantia nigra. Approximately 900,000 people in the United States have Parkinson's disease. Symptoms progress slowly over years and differ from person to person. The general symptoms of Parkinson's disease include tremor, bradykinesia, limb rigidity, gait and balance problems. Parkinson's disease itself is not fatal, but related complications are the 14th leading cause of death in the United States per the CDC.

Dosage Form [2]

Inbrija is available as an inhalation powder via 42 mg capsules for use with Inbrija inhaler.

Manufacturer [2]

Distributed by: Acorda Therapeutics, Inc., Ardsley, NY 10502.

Indication(s) [2]

Inbrija is indicated for the intermittent treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa.

Clinical Efficacy [2,3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Levodopa, the metabolic precursor or dopamine, crosses the blood brain barrier and presumably is converted to dopamine in the brain.

Pharmacokinetics:

	Inbrija
Absorption	Time to peak: 0.5 hours
Metabolism	Extensively metabolized via two major metabolic pathways: decarboxylation by dopa decarboxylase, and O-methylation by catechol-O-methyltransferase (COMT)
Excretion	Urine: has not been evaluated Feces: has not been evaluated
Half-life	2.3 hours

Clinical Trials Experience

STUDY 1 DESIGN	Randomized, double-blind, placebo-controlled study (n = 351)

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INCLUSION CRITERIA	• Idiopathic Parkinson's Disease (PD) diagnosed between the ages of 30 and 85 • Hoehn and Yahr stage 1-3 in an "on" stage • Require levodopa-containing medication regimen at least 3 times during the waking day • Experience motor fluctuations with a minimum of 2 hours of average daily "off" time per waking day (excluding early morning "off" time and demonstrate levodopa responsiveness • Are on stable PD medication regimen • Total daily levodopa dose <1600 mg/day • Able to perform a spirometry maneuver in the ON and OFF states • Normal cognition confirmed by MMSE score ≥ 25
EXCLUSION CRITERIA	• Pregnant or lactating females • Previous surgery for PD or plan to have stereotactic surgery during the study period • History of psychotic symptoms • Known contraindication to use of levodopa • Any contraindication to performing routine spirometry
TREATMENT REGIMEN	Patients were randomized to receive Inbrija low dose (42 mg) (n=113), Inbrija high dose (84 mg) (n=114) or placebo (n=112) inhalational powder used up to 5 times/day for OFF episodes for 12 weeks.
RESULTS	The primary measure of efficacy was the change from predose in the UPDRS Part III score to 30 minutes post dose at week 12. The mean UPDRS scores at screening in the ON state were 14.9 for patients randomized to Inbrija, and 16.1 randomized to placebo. At week 12, the mean reduction in the motor scores were -5.9 (95% CI -8.86 to -2.96) for placebo and -9.8 (-12.79 to -6.87) for the Inbrija group. The mean difference was -3.92 (p=0.0088). The proportion of patients who returned to the ON state and sustained that ON through 60 minutes post-dose was 58% for the Inbrija and 36% for the placebo (p=0.003). Treatments were safe and tolerated.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [2]

- Concurrent use of a nonselective monoamine oxidase (MAO) inhibitor or recent use of a MAO inhibitor (2 weeks).

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Warnings and Precautions [3,4]

- May cause falling asleep during activities of daily living
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion.
- Hallucinations/ exacerbation of psychosis may occur. Should not be used in major psychotic disorders
- Impulse control disorders: consider dose reduction
- May cause or exacerbate dyskinesia
- Not recommended in patients with asthma, COPD, or other chronic underlying lung disease
- May increase intraocular pressure in patients with glaucoma
- May elevate liver function tests

Adverse Effects [3,4]

Most common, ≥ 2%	Inbrija (n = 114) %
Cough	15
Upper respiratory tract infections	6
Sputum discolored	5
Nausea	5
Dyskinesia	4
Vomiting	3
Falls	3
Nasopharyngitis	3
Nasal discharge discoloration	2
Oropharyngeal pain	2
Bronchitis/pneumonia	2
Lacerations/Skin abrasion	2
Chest discomfort	2
Headache	2
Insomnia	2
Orthostatic hypotension	2
Pain in extremities	2
Blood bilirubin increased	2
Red blood cell count decreased	2

Drug Interactions [3,4]

- Monitor patients on MAO-B inhibitors for orthostatic hypotension
- Dopamine D2 antagonists, isoniazid, and iron salts- may reduce the effectiveness of Inbrija

Dosage and Administration [3,4]

- Administered via oral inhalation when symptoms of an off period start to return.
- The recommended dosage is two 42 mg (84 mg) capsules as needed, up to 5 times daily.
- Maximum dose per off period is 84 mg, and the maximum daily dosage is 420 mg.

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Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Levodopa	Inbrija	Acorda	84 mg up to 5 times/day	$949.80 per inhaler and 60 capsules

** Wholesale Acquisition Cost

Conclusion

Inbrija is indicated for the intermittent treatment of OFF episodes in patients with Parkinson's Disease treated with carbidopa/levodopa. The efficacy of Inbrija was demonstrated in one randomized, double-blind, placebo-controlled clinical trial in 114 patients. There was a statistically significant difference in the change in the predose UPDRS Part III score to 30 minutes post dose after 12 weeks between Inbrija and placebo. The most common adverse reactions in patients taking Inbrija (>5%) were cough and upper respiratory tract infections.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Parkinson's Foundation. https://www.parkinson.org. Accessed May 27, 2019.
2) Product Information: Inbrija™ (levodopa). Acorda Therapeutics, Inc., Ardsley, NY 10502.
3) Inbrija: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
4) Inbrija: Package Insert. Available from: www.accessdata.fda.gov. Accessed May 27th, 2019.
5) A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of CVT301 in Parkinson's Disease Patients with Motor Response Fluctuations (OFF Phenoma. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT02240030?term=02240030&rank=1.

Prepared by: Jaci Schowengerdt, PharmD

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