

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Amantadine Extended-Release Drugs

- Gocovri™ (amantadine extended-release capsules – Adamas Pharma)
- Osmolex ER™ (amantadine extended-release tablets – Vertical Pharmaceuticals)

TAC APPROVAL DATE: 12/19/2018

OVERVIEW

Gocovri is indicated for the treatment of dyskinesia in patients with Parkinson's disease (PD) receiving levodopa-based therapy, with or without concomitant dopaminergic medications.¹ The initial daily dosage of Gocovri is 137 mg once daily (QD) at bedtime. After one week, increase to the recommended dosage of 274 mg (equivalent to 340 mg amantadine hydrochloride) QD at bedtime. Gocovri is available in 68.5 mg and 137 mg strengths (as 85 mg or 170 mg amantadine hydrochloride, respectively).

Osmolex ER is indicated for the treatment of Parkinson's disease and for the treatment of drug-induced extrapyramidal reactions in adult patients.² The recommended initial dosage of Osmolex ER is 129 mg QD in the morning. The dosage may be increased in weekly intervals to a maximum daily dose of 322 mg (administered as a 129 mg and 193 mg tablet), taken in the morning. For patients unable to tolerate more than 100 mg/day of immediate-release (IR) amantadine, there is no equivalent dose or dosing regimen of Osmolex ER. Osmolex ER is available in 129 mg, 193 mg, and 258 mg strengths (as 160 mg, 240 mg, or 320 mg amantadine hydrochloride, respectively).

Amantadine hydrochloride is available as an IR 100 mg capsule, 100 mg tablet, and 50 mg/5 mL oral solution. The amantadine IR products are indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus; idiopathic PD [Paralysis Agitans], postencephalitic parkinsonism, symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication, and in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis; and drug-induced extrapyramidal reactions.³⁻⁵ For the treatment of PD, the usual dose of amantadine IR is 100 mg twice daily (BID) when used alone. An initial dose of amantadine IR is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs; the dose may be increased to 100 mg BID, if necessary. Patients initially deriving benefit from amantadine may experience a fall-off of effectiveness after a few months; benefit may be regained by increasing the dose to 300 mg/day in divided doses. Occasionally, patients whose responses are not optimal with amantadine IR 200 mg daily may benefit from an increase up to 400 mg/day in divided doses. For the treatment of drug-induced extrapyramidal reactions, the usual dose of amantadine IR is 100 mg BID. Occasionally, patients whose responses are not optimal with amantadine IR 200 mg/day may benefit from an increase up to 300 mg/day in divided doses.

Disease Overview

PD is a common neurodegenerative disease and is a chronic, progressive disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system.^{6,7} An estimated 50,000 Americans are diagnosed each year with PD and it is estimated that 1 million people in the US have the condition. PD typically affects patients who are greater than 60 years of age.⁸ Its characteristic features include resting tremor, rigidity, bradykinetic movements, and postural instability.^{6,7} As these symptoms become more pronounced, patients with PD may have difficulty walking, talking, or

completing other simple tasks. Early symptoms of PD are subtle and occur gradually. The disease course varies considerably as well as the intensity of symptoms. While some patients become severely disabled, others experience only minor motor disruptions. Resting tremor is the major symptom for some individuals, while for others tremor is only a minor complaint and other manifestations may be more troublesome. It is not possible to predict which symptoms will affect an individual. PD symptoms are thought to be related to depletion of dopamine in the corpus striatum. Use of dopamine is ineffective in the treatment of PD because it does not penetrate the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier and is believed to be converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves PD symptoms. Other medications are also utilized to improve mobility.

Although initially effective, dopaminergic therapies are eventually complicated by motor fluctuations, including “off” time (periods during which PD symptoms return when the medication effect wears off) and dyskinesia (drug-induced involuntary movements, e.g., chorea and dystonia) in most patients.⁹ These motor complications can impair patient quality of life and cause substantial disability. Risk factors for motor complications include younger age at the onset of PD, increased disease severity, higher levodopa dosage, and longer disease duration. These problems are often addressed with levodopa adjustments and the addition of adjunctive medications.

Clinical Efficacy

Gocovri was assessed in two randomized, double-blind, placebo-controlled efficacy trials, EASE LID (n = 121) and EASE LID 3 (n = 75), in patients with PD and dyskinesia.¹ In both studies, the primary efficacy endpoint was the change in total score of the Unified Dyskinesia Rating Scale (UDysRS) between baseline and Week 12. Patients in EASE LID and EASE LID 3 were treated with a stable dose of levodopa, with 32% of patients on levodopa monotherapy; 54% of patients and 44% of patients were treated with concomitant dopamine agonists and/or MAO-B inhibitors, respectively. In EASE LID and EASE LID 3, a significant decrease in mean UDysRS total score (reduction in dyskinesia) was observed at Week 12 in patients treated with Gocovri compared with placebo (EASE LID treatment difference: -7.9; P = 0.0009 and EASE LID 3 treatment difference: -14.4; P < 0.0001). Gocovri has not been compared with amantadine IR or other active treatments in clinical trials.

No clinical efficacy studies were undertaken for approval of Osmolex ER.² The efficacy of Osmolex ER is based upon bioavailability studies comparing Osmolex ER with IR amantadine.

Guidelines

The 2006 American Academy of Neurology (AAN) guideline on the treatment of PD with motor fluctuations and dyskinesia recommends considering the use of amantadine in patients with PD and motor fluctuations to reduce dyskinesia (Level C).⁹ The authors concluded that amantadine IR (given as 100 mg BID) is possibly effective in reducing dyskinesia based on one Class II study. The guidelines have not been updated to include Gocovri or Osmolex ER.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of amantadine extended-release products. Because of the specialized skills required for evaluation and diagnosis of patients treated with amantadine extended-release as well as the monitoring required for adverse events and long-term efficacy, initial approval requires amantadine extended-release to be prescribed by or in consultation

with a physician who specializes in patients with PD. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

- I. Coverage of Gocovri is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Dyskinesia in Parkinson's Disease (PD).** Approve for the duration noted below if patient meets ONE of the following (A or B):

- A) Initial Therapy. Approve Gocovri for 3 months if the patient meets the following criteria (i, ii, and iii):

- i. Gocovri is prescribed by or in consultation with a neurologist; AND
- ii. Patient is currently receiving levodopa-based therapy (e.g., carbidopa/levodopa); AND
- iii. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
 - a) Patient derived benefit from IR amantadine but had intolerable adverse events, as determined by the prescriber; OR
 - b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber.

- B) Patients Currently Receiving Gocovri. Approve Gocovri for 1 year if the patient meets the following criteria (i, ii, iii, and iv):

- i. Gocovri is prescribed by or in consultation with a neurologist; AND
- ii. Patient is currently receiving levodopa-based therapy (e.g., carbidopa/levodopa); AND
- iii. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
 - a) Patient derived benefit from IR amantadine but had intolerable adverse events, as determined by the prescriber; OR
 - b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
- iv. Patient has had a response to therapy (e.g., decrease in dyskinesia), as determined by the prescriber.

The amantadine IR products are indicated for idiopathic PD [Paralysis Agitans], postencephalitic parkinsonism, symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication, and in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis; drug-induced extrapyramidal reactions; and the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus;³⁻⁵

- II. Coverage of Osmolex ER is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Parkinson's Disease (PD). Approve for the duration noted below if patient meets ONE of the following (A or B):

A) Initial Therapy. Approve Osmolex ER for 3 months if the patient meets the following criteria (i and ii):

- i. Osmolex ER is prescribed by or in consultation with a neurologist; AND
- ii. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
 - a) Patient derived benefit from IR amantadine but had intolerable adverse events, as determined by the prescriber; OR
 - b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber.

B) Patients Currently Receiving Osmolex ER. Approve Osmolex ER for 1 year if the patient meets the following criteria (I, ii, and iii):

- i. Osmolex ER is prescribed by or in consultation with a neurologist; AND
- ii. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
 - a) Patient derived benefit from IR amantadine but had intolerable adverse events, as determined by the prescriber; OR
 - b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
- iii. Patient has had a response to therapy (e.g., decrease in dyskinesia), as determined by the prescriber.

The amantadine IR products are indicated for idiopathic PD [Paralysis Agitans], postencephalitic parkinsonism, symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication, and in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis; drug-induced extrapyramidal reactions; and the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus;³⁻⁵

2. Drug-Induced Extrapyramidal Reactions. Approve for the duration noted below if patient meets ONE of the following (A or B):

A) Initial Therapy. Approve Osmolex ER for 3 months if the patient meets the following criteria (i and ii):

- i. Osmolex ER is prescribed by or in consultation with a neurologist; AND
- ii. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
 - a) Patient derived benefit from IR amantadine but had intolerable adverse events, as determined by the prescriber; OR
 - b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber.

B) Patients Currently Receiving Osmolex ER. Approve Osmolex ER for 1 year if the patient meets the following criteria (i, ii, and iii):

- i. Osmolex ER is prescribed by or in consultation with a neurologist; AND
- ii. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
 - a) Patient derived benefit from IR amantadine but had intolerable adverse events, as determined by the prescriber; OR

- b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
- iii. Patient has had a response to therapy (e.g., decrease in extrapyramidal reactions), as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Amantadine extended-release products have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gocovri™ extended-release capsules [prescribing information]. Emeryville, CA: Adamas Pharma LLC; August 2017.
2. Osmolex ER™ extended-release tablets [prescribing information]. Bridgewater, NJ: Vertical Pharmaceuticals, LLC.; February 2018.
3. Amantadine capsules [prescribing information]. Bridgewater, NJ: Alembic Pharmaceuticals, Inc.; April 2017.
4. Amantadine tablets [prescribing information]. Parsippany, NJ: Actavis Pharma, Inc.; January 2017.
5. Amantadine oral solution [prescribing information]. Amityville, NY: Hi-Tech Pharmacal Co., Inc.; July 2016.
6. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease. A review. *JAMA*. 2014;311(16):1670-1683.
7. National Institute of Neurological Disorders and Stroke (NINDS) Parkinson's disease information page. Available at: <https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page>. Accessed on December 10, 2018.
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9. Pahwa R, Factor SA, Lyons KE, et al. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66(7):983-995.

OTHER REFERENCES UTILIZED

- Pahwa R, Tanner CM, Hauser RA. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial. *JAMA Neurol*. 2017;74(8):941-949.
- Oertel W, Eggert K, Pahwa R. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). *Mov Disord*. 2017 Aug 21. [Epub ahead of print].
- Wagle Shukla A. Extended-Release Amantadine-A Smart Pill for Treatment of Levodopa-Induced Dyskinesia but Does the Evidence Justify the Cost? *JAMA Neurol*. 2017;74(8):904-905.
- Hauser RA, Pahwa R, Tanner CM. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson's Disease (EASE LID 2 Study): Interim Results of an Open-Label Safety Study. *J Parkinsons Dis*. 2017;7(3):511-522.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	12/20/2017
Selected revision	Changed policy name to Amantadine Extended-Release Drugs (formerly Gocovri) PA Policy. Added Osmolex ER to the policy with approval criteria for its two FDA-approved uses: Parkinson's disease and Drug-Induced Extrapyrimaldal Reactions. Changed the name of the approved indication for Gocovri from Dyskinesia in Patients with Parkinson's Disease to Dyskinesia in Parkinson's Disease. Added requirement of previous immediate-release amantadine use for approval of continuation of therapy for Gocovri.	06/06/2018
Annual revision	No change to criteria.	12/19/2018
DEU revision	1/16/2019: Addition of "Parkinson's Disease" to the title of the policy.	--

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.