CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January - February

BRAND NAME
Gocovri™

GENERIC NAME
Amantadine (extended-release)

MANUFACTURER
Adamas Pharma, LLC

DATE OF APPROVAL
August 24, 2017

PRODUCT LAUNCH DATE
Fourth quarter of 2017

REVIEW TYPE
☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)[1]
New Indication
Gocovri is indicated for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

Current Indication(s)
Previous indications for immediate-release amantadine include treatment and prophylaxis of influenza A, Parkinson's disease, and drug-induced extrapyramidal reactions.

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Immediate-release amantadine is indicated for the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, amantadine is less effective than levodopa, (-)-3-(3,4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established.

OFF LABEL USES
Not applicable

CLINICAL EFFICACY
Background
Dyskinesia is levodopa-related, abnormal, involuntary movements caused by an excess amount of levodopa. However, it can occur at a therapeutic dose and does not represent overdose. Dyskinesia is common in patients with young-onset Parkinson's disease (disease onset before the age of 50 years) and long-term use of levodopa (may also occur with dopamine agonists).

	Oertel W, et al. Randomized, EASE LID 3[2]
Study Design	Phase 3, randomized, double-blind, placebo-controlled trial
N	75
Drug Regimen	Gocovri 137 mg PO QD for one week, then 274 mg PO QD from weeks 2 through 12 (N=37) or placebo (N=38)
Primary Outcome(s)	Change from baseline to week 12 on the Unified Dyskinesia Rating Scale (UDysRS) total score in the modified intent-to-treat population
Secondary Outcome(s)	Change from baseline to week 12 in ON time without troublesome dyskinesia and OFF time
Results	Primary endpoint (change from baseline in UDysRS total score): Placebo: -6.3 (SE of 2.1) Amantadine: -20.7 (SE of 2.2) Treatment difference, 95% CI: -14.4 (-20.4 to -8.3); p<0.0001 Secondary endpoint (ON time without troublesome dyskinesia and OFF time): ON time: Placebo: 2.1 (SE of 0.5) Amantadine: 4.0 (SE of 0.6) Treatment difference, 95% CI: 1.9 (0.4 to 3.5); p=0.0168 OFF time: Placebo: 0.6 (SE of 0.3) Amantadine: -0.5 (SE of 0.3) Treatment difference, 95% CI: -1.1 (-2.0 to -0.2); p=0.0199

<table>
<tr><td></td><td></td></tr>
<tr><td># Withdrew due to Lack of Efficacy</td><td>Not reported</td></tr>
<tr><td># Withdrew due to Adverse Effects</td><td>Two patients in the placebo group and 6 patients in the treatment group reported study-drug related adverse effects.</td></tr>
<tr><td></td><td>Pahwa, et al. EASE LID Study[3]</td></tr>
<tr><td>Study Design</td><td>Phase 3, randomized, double-blind, placebo-controlled trial</td></tr>
<tr><td>N</td><td>121</td></tr>
<tr><td>Drug Regimen</td><td>Gocovri 137 mg PO QD for one week then 274 mg PO QD from weeks 2 through 25 (N=63) or placebo (N=58)</td></tr>
<tr><td>Primary Outcome(s)</td><td>Change from baseline to week 12 on the UDysRS total score in the modified intent-to-treat population</td></tr>
<tr><td>Secondary Outcome(s)</td><td>1. Change from baseline to week 24 on the UDysRS total score
2. Change from baseline to week 12 in ON time without troublesome dyskinesia and OFF time at 12 and 24 weeks</td></tr>
<tr><td>Results</td><td><u>Primary endpoint (change from baseline in UDysRS total score at week 12):</u>
Placebo: -8.0 (SE of 1.6)
Amantadine: -15.9 (SE of 2.2)
Treatment difference, 95% CI: -7.9 (-12.5 to -3.3); p<0.001

<u>Secondary endpoint (change from baseline in UDysRS total score at week 24):</u>
Placebo: -6.3 (SE of 1.9)
Amantadine: -15.6 (SE of 1.9)
Treatment difference, 95% CI: -9.3 (-14.7 to -4.0); p<0.001

<u>Secondary endpoint (ON time without troublesome dyskinesia and OFF time):</u>
<table>
<tr><th></th><th>Placebo (SE)</th><th>Amantadine (SE)</th><th>Treatment difference (95% CI); p value</th></tr>
<tr><td colspan="4">ON time</td></tr>
<tr><td>Week 12</td><td>0.9 (0.4)</td><td>3.6 (0.4)</td><td>2.8 (1.6 to 4.0); p<0.001</td></tr>
<tr><td>Week 24</td><td>1.4 (0.5)</td><td>3.6 (0.4)</td><td>2.2 (1.0 to 3.5); p<0.001</td></tr>
<tr><td colspan="4">OFF time</td></tr>
<tr><td>Week 12</td><td>0.3 (0.3)</td><td>-0.6 (0.3)</td><td>-0.9 (-1.6 to -0.2); p=0.02</td></tr>
</table></td></tr>
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	Week 24	0.2 (0.3)	-0.6 (0.3)	-0.8 (-1.6 to -0.0); p=0.04
# Withdrew due to Lack of Efficacy	Not reported			
# Withdrew due to Adverse Effects	Seven patients in the placebo group and 40 patients in the treatment group reported study-drug related adverse effects.			

CONTRAINDICATIONS
Gocovri is contraindicated in patients with end-stage renal disease.

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
Gocovri interacts with other anticholinergic drugs. Dose reductions are recommended if atropine-like effects occur. Gocovri interacts with drugs affecting urinary pH (such as carbonic anhydrase inhibitors and sodium bicarbonate). Gocovri excretion increased with acidic urine and there may be possible accumulation with alkaline urine. Administration of live attenuated influenza vaccine is not recommended while taking Gocovri due to the antiviral properties of amantadine (inactivated influenza vaccines may be used). Lastly, Gocovri interacts with alcohol due to the increased potential for CNS effects such as dizziness, confusion, lightheadedness and orthostatic hypotension.

ADVERSE REACTIONS
The most commonly observed adverse reactions occurring at a frequency of 10% and greater than placebo were hallucinations, dizziness, dry mouth, peripheral edema, constipation, fall and orthostatic hypotension.

DOSAGE AND ADMINISTRATION
The initial daily dosage is 137 mg orally at bedtime; after 1 week, increase to the recommended daily dosage of 274 mg. A lower dose is recommended in patients with moderate to severe renal impairment.

PRODUCT AVAILABILITY
Extended-release capsules: 68.5 mg and 137 mg

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THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
amantadine immediate-release	Initial dosing is 100 mg PO QD; titrate as needed, up to 100 mg PO QID	Off-label usage

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation
• There is not significant potential for inappropriate use.
Product Comparison
• Equal therapeutic outcomes are anticipated for immediate-release amantadine and Gocovri; therefore, it would be clinically appropriate to provide equal access to both or to require a trial of one before the other.

REFERENCES

[1] Gocovri Prescribing Information. Emeryville, CA; Adamas Pharma, LLC: August 2017. Available at: www.gocovri.com. Accessed October 17, 2017.
[2] Oertel W, Eggert Karla, Pahwa R, et al. 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 August 21; available at doi: 10.1002/mds.27131.
[3] Pahwa R, Tanner CM, Hauser RA, et al. ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in parkinson disease (EASE LID Study). JAMA Neurol. 2017;74(8):941-949. Doi:10.100/jamaneurol.2017.0943.

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