

Clinical Policy: Memantine, Memantine/Donepezil (Namenda, Namenda XR, Namzaric)

Reference Number: AZ.CP.PHAR.29

Effective Date: 11.16.16

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Line of Business: Arizona Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Memantine (Namenda[®], Namenda XR[®]) is an oral, non-competitive NMDA receptor antagonist. Namzaric[®] is an oral combination of donepezil and memantine extended release.

FDA approved indication

Memantine (Namenda, Namenda XR) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

Namzaric is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on memantine and donepezil.

Policy/Criteria

Provider *must* submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with Centene Corporation[®] that Namenda, Namenda XR, Namzaric are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Moderate Dementia (must meet all):

1. Diagnosis of moderate dementia of the Alzheimer's type, including supporting documentation of one of the following (a or b):
 - a. Mini Mental Status Examination (MMSE) score between 12 and 21;
 - b. Both of the following (i and ii):
 - i. Baseline ADAS-Cog or ADCS-ADL score;
 - ii. Failure of donepezil OR rivastigmine (at up to maximally indicated doses) unless contraindicated or clinically significant adverse effects are experienced. Therapeutic failure is defined as one of the following:
 1. MMSE score declines by more than 5 points over successive evaluations
 2. MMSE score falls below 12
 3. ADAS-Cog score increases by 3 or more over successive evaluations
 4. ACDS-ADL increases by 5 or more over successive evaluations
 5. Intolerance to therapy despite dose reduction;
2. For Namzaric requests, medical justification must be provided why individual generic components of donepezil and memantine cannot be used;

3. Dose does not exceed the FDA approved maximum recommended dose for the relevant drug, indication.

Approval duration: 12 months

B. Severe Dementia (must meet all):

1. Diagnosis of severe dementia of the Alzheimer's type, including supporting documentation including one of the following:
 - a. MMSE score between 3 and 11
 - b. Baseline or current ADAS-Cog or ACDS-ADL score;
2. For Namzaric requests, medical justification must be provided why individual generic components of donepezil and memantine cannot be used;
3. Dose does not exceed the FDA approved maximum recommended dose for the relevant drug, indication.

Approval duration: 12 months

C. Other diagnoses/indications

1. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Moderate to Severe Dementia (must meet all):

1. Currently receiving medication via a health plan affiliated with Centene Corporation or member has previously met initial approval criteria;
2. Documentation of positive response to therapy including clinical stability and/or improvement.
3. Discontinuation of therapy will be recommended based on one of the following:
 - a. MMSE score decline > 5 points over successive evaluations
 - b. MMSE score is below 3
 - c. ADAS-cog score increases by 3 over successive evaluations
 - d. ACDS-ADL increases by 5 or more over successive evaluations;
4. If request is for a dose increase, new dose does not exceed the FDA approved maximum recommended dose for the relevant drug, indication.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Centene Corporation and documentation supports positive response to therapy.

Approval duration: Duration of request or 12 months (whichever is less); or

2. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – CP.PMN.53 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ADAS-Cog: Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Score
ASD: Autism Spectrum Disorder
BID: twice daily

CNS: central nervous system
IR: immediate release
MMSE: Mini Mental Status Examination
NMDA: N-methyl-D-aspartate
PO: by mouth
XR: extended release

Appendix B: General Information

- Memantine is thought to act by blocking the actions of glutamate, the principal excitatory neurotransmitter in the CNS. The effects of glutamate are mediated by different receptor types, including NMDA receptors, which play a role in physiologic processes such as learning and memory formation. Persistent activation of NMDA receptors by glutamate has been implicated as a possible cause of neurodegeneration in various types of dementia, including dementia of the Alzheimer's type (Alzheimer's disease), and is thought to contribute to the symptomatology of Alzheimer's disease. In vitro studies have shown that β -amyloid, which accumulates to form amyloid plaques in patients with Alzheimer's disease, increases the release of glutamate upon neuronal depolarization, supporting a role for pathologic NMDA receptor activation in the disease. It has been postulated that low- to moderate-affinity NMDA receptor antagonists may prevent glutamate-induced neurotoxicity without interfering with the physiologic processes mediated by the activation of NMDA receptors. However, there currently is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.
- Memantine is not indicated for use in infants, children or adolescents. Memantine failed to demonstrate efficacy in two 12 week controlled trials of patients 6-12 years of age with autism spectrum disorders (ASD), including Asperger's disorder.
- MMSE differences between placebo and Namenda were not demonstrated in clinical trials. This may have been due to a number of reasons including the sensitivity of the MMSE or the duration of the trials.
- ADAS-cog and ACDS-ADL have been used as reliable measures of drug efficacy for other agents for Alzheimer's dementia. Therefore, ADAS-cog and ACDS-ADL have been chosen as accepted measures of Namenda's efficacy for reauthorization of coverage.
- American Psychiatric Association practice guidelines for the treatment of Alzheimer's addresses combination therapy with a cholinesterase inhibitor as follows, "Therapeutic benefits are also observed when memantine is administered to patients already receiving a stable regimen of donepezil."
- Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of Memantine
- Namenda XR can be taken with or without food. Namenda XR capsules can be taken intact or may be opened, sprinkled on applesauce, and thereby swallowed. The entire contents of each capsule should be consumed; the dose should not be divided.
- It is recommended that a patient who is on a regimen of 10 mg twice daily of memantine be switched to NAMENDA XR 28 mg once daily capsules the day following the last

dose of 10 mg memantine. Patients with renal impairment receiving 5mg twice daily of the immediate release tablets may be converted to the XR capsule at a dose of 14mg once daily after the last dose of the IR tablet.

- MMSE is an eleven question, 30 point exam that is used to determine level of cognitive impairment. It should be used in conjunction with other behavioral and psychological tests to assess patients. Score interpretations: 24-30 no cognitive impairment, 18-23 mild cognitive impairment, 0-17 severe cognitive impairment.
- For patients stabilized on donepezil alone, 7mg-10mg once daily is the recommended starting dose, increased in 7mg increments no sooner than weekly up to 28mg-10mg dose. For patients stabilized on donepezil and memantine (10mg bid or 28mg XR QD), can be switched to 28mg-10mg XR capsule once daily. Namzaric can be taken with or without food. The capsules can be taken intact or may be opened or sprinkled on applesauce and swallowed without chewing.

Appendix C: Therapeutic Alternatives

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
Donepezil (Aricept, Aricept ODT)	5mg daily at bedtime. If no response after 4-6 weeks, may titrate dose to 10mg daily. If no improvements after 4-8 weeks, consider discontinuation of therapy.	23mg per day
Galantamine (Razadyne)	4mg BID, titrate as tolerated with a minimum of 4 weeks between dose increases, to 8mg BID and 12mg BID	24mg per day
Galantamine ER (Razadyne ER)	8mg per day, titrate to 16mg per day over 4 weeks up to 24mg per day	24mg per day
Rivastigmine (Exelon)	Oral: 1.5mg BID, titrate as tolerated with a minimum of 2 weeks between dose increases, to 3mg BID, 4.5mg BID and 6mg BID. Transdermal: 4.6mg/24hour topically QD. May titrate to effectiveness after a minimum of 4 weeks on each dose up to 13.3mg/24hour.	12mg per day 13.3mg/24 hour patch once daily

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.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Memantine (Namenda)	5mg PO daily. Increase by 5mg per day in divided doses at one-week intervals to a maximum of 10mg	10mg PO BID

	BID	
Namenda XR (memantine XR)	7mg PO daily, increase by 7mg per day at one week intervals to the recommended dose of 28mg PO once daily. 14mg once daily is the recommended maintenance dose in patients with severe renal impairment (CrCl 5-29mL/min)	28mg PO QD
Namzaric (memantine XR and donepezil)	Initially, 7mg/10mg once daily in the evening. Dose should be increased in 7mg increments (at least 1 week between adjustments) to the recommended dose of 28 mg /10 mg PO QD in the evening. Severe Renal Impairment (CrCl 5-29 mL/min): One 14 mg memantine/10 mg donepezil capsule PO QD	28mg memantine/ 10mg donepezil once daily

VI. Product Availability

Drug	Availability
Memantine (Namenda)	Tablets: 5mg, 10mg Blister titration pack: 28x5mg and 21 x10mg tablets Solution: 2mg/ml
Namenda XR (memantine)	XR Capsules: 7mg, 14mg, 21mg, 28mg, titration pack
Namzaric (memantine XR, donepezil)	XR Capsules: 7mg/10mg, 14mg/10mg, 21mg/10mg, 28mg/10mg Titration Pack: (7mg, 14mg, 21mg, 28mg) -10mg

VII. References

1. Namenda® [Prescribing Information] St. Louis, MO: Forest Pharmaceuticals Inc; October 2013.
2. Namenda XR® [Prescribing Information] St. Louis, MO: Forest Pharmaceuticals Inc; September 2014.
3. Razadyne [Prescribing information] Titusville, NJ; Janssen Pharmaceuticals. February 2017.
4. Aricept [Prescribing information] Woodcliff Lake, NJ: Eisai; July 2015.

5. Exelon® [Prescribing Information] East Hanover, NJ: Novartis Pharmaceuticals; November 2016.
6. Trinh NH, Hoblyn J, Mohanty S and Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer Disease. JAMA 2003;289:2:210-216.
7. Blacker CV, Greenwood DT, Wesnes KA, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized, controlled trial. JAMA 2004;292(10):1195-204.
8. Tariot PN, Farlow MR, Grossberg GT, et al for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer Disease already receiving donepezil; A Randomized controlled trial. JAMA 2004;291:3:317-324.
9. Rabins PV (2007). Guideline watch: Practice guideline for the treatment of patients with Alzheimer’s disease and other dementias, Second Edition. Arlington, VA: American Psychiatric Association. Available online at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimers.pdf Accessed June 24, 2016.
10. Peskind ER, Potkin SG, Pomara N, et al. Memantine treatment in mild to moderate disease: a 24-week randomized, controlled trial. Am J Geriatr Psych.2006;14(8):704-15.
11. The American Geriatrics Society. A Guide to Dementia Diagnosis & Treatment. Available at: <http://www.americangeriatrics.org/> . Accessed June 6, 2017.
12. AHFS Drug Information Updates. Available at <http://www.ahfsdruginformation.com>. Accessed June 6, 2017.
13. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed June 6, 2017.
14. Philippe R, Steven F, Serge G, et al. Review of Alzheimer's disease scales: is there a need for a new multi-domain scale for therapy evaluation in medical practice? Alzheimers Res Ther. 2010; 2(4): 24. Published online 2010 August 26.
15. Namenda® oral solution [Prescribing Information] St. Louis, MO: Forest Pharmaceuticals Inc; August 2014.
16. Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. Hosp Pract. 1987;22(1A):99, 103, 106,110.
17. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimer’s & Dementia. 2011;7(3): 263-269.
18. Namzaric [Prescribing Information] Cincinnati, OH: Forest Pharmaceuticals Inc; July 2016.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template; minor changes to verbiage and grammar. References updated. Added Namzaric to criteria.	06.02.17	11.17
Reviewing, renumbered and rebranded for AzCH.	09.13.18	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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CLINICAL POLICY

Memantine, Memantine/Donepezil



Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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