Clinical Policy: Acetylcholinesterase Inhibitors (Aricept, Aricept ODT, Razadyne, Razadyne ER, Exelon, Exelon Patch)

Reference Number: AZ.CP.PHAR.1018
Effective Date: 11.16.16
Last Review Date: 02.22
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following are cholinesterase inhibitors requiring prior authorization: donepezil (Aricept®, Aricept ODT®), galantamine (Razadyne®, Razadyne ER®), rivastigmine (Exelon®, Exelon Patch®).

AHCCCS preferred drugs in this class include: Aricept, Aricept ODT, Razadyne, Razadyne ER

AHCCCS non-preferred drugs in this class include: Exelon®, Exelon Patch®

FDA approved indication
Aricept, Aricept ODT are indicated for the treatment of dementia of the Alzheimer's type

Razadyne, Razadyne ER are indicated for the treatment of mild to moderate dementia of the Alzheimer's type

Exelon, Exelon Patch are indicated:
- For the treatment of dementia of the Alzheimer's type
- For the treatment of mild to moderate dementia associated with Parkinson's disease

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 Arizona Complete Health-Complete Care Plan and Care1st that Aricept, Aricept ODT, Exelon, Exelon Patch, Razadyne, Razadyne ER are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
A. Alzheimer's Dementia (must meet all)**:**
1. Diagnosis of mild to severe dementia;
2. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

3. For donepezil ODT, rivastigmine, rivastigmine patch, galantamine ER member must meet one of the following (a or b):
   a. Failure of ≥ 3 month trial of donepezil at doses ≥ 10 mg per day or galantamine 24 mg per day, unless contraindicated or clinically significant adverse effects are experienced;
   b. If member cannot take donepezil and galantamine due to intolerance or contraindication(s), failure of ≥ 3 month trial of memantine at doses ≥ 20 mg/day, unless contraindicated or clinically significant adverse effects are experienced;

Approval duration: 12 months

B. Parkinson's Disease Dementia (must meet all)**:**
1. Diagnosis of mild to moderate dementia associated with Parkinson's Disease
2. Request is for rivastigmine:
   a. Failure of ≥ 3 month trial of donepezil at doses ≥ 10 mg per day unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 12mg per day for rivastigmine or 23mg for donepezil

Approval duration: 12 months

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

II. Continued Therapy

A. Alzheimer's 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. If request is for a dose increase, new dose does not exceed applicable FDA approved dosage.

Approval duration: 12 months

B. Parkinson's 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. If request is for a dose increase, new dose does not exceed applicable FDA approved dosage.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

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- AZ.CP.PMN.53 for Arizona Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

COPD: chronic obstructive pulmonary disease
FDA: Food and Drug Administration
MMSE: Mini Mental Status Examination
XR: extended release

Appendix B: General Information

- Aricept, Aricept ODT, Exelon and Razadyne are acetylcholinesterase inhibitors which are likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. They may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block. Patients should be monitored closely for symptoms of active or occult GI bleeding, especially for patients at risk for developing ulcers. Patients with a history of asthma or COPD should be monitored closely.
- Dose related nausea and vomiting is a common side effect of donepezil. This effect is usually transient, sometimes lasting one to three weeks. There is higher incidence of peptic ulcer disease and gastrointestinal bleeding associated with cholinesterase inhibitors and patients should be monitored appropriately. Dose dependent weight loss with the use of donepezil has also been reported.
- Consider dosage adjustments of Exelon for mild to moderate hepatic impairment and weight less than 50kg. Gastrointestinal adverse reactions: May include significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss, and may necessitate treatment interruption. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. Concomitant use with metoclopramide, beta-blockers, or cholinomimetics and anticholinergic medications is not recommended.
- Razadyne is metabolized by both the liver and kidney. Dose should not exceed 16 mg/day for moderate hepatic impairment; do not use in patients with severe hepatic impairment. Renal impairment: should not exceed 16 mg/day for creatinine clearance 9-59 mL/min; do not use in patients with creatinine clearance less than 9 mL/min.

- In a randomized double blind placebo controlled trial in 434 patients with chronic fatigue syndrome, there was no significant difference between Razadyne (galantamine) and placebo for Clinician Global Impression Scale or any of the secondary outcome measures.
- 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.

Appendix C: Therapeutic Alternatives

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
For patients with moderate to severe dementia of the Alzheimer's type		
Memantine, memantine-donepezil (Namenda®, Namenda XR® Namzaric XR®)	IR: Administer 5 mg PO QD initially. Increase at one-week intervals in 5 mg increments up to 20mg per day. XR: 7mg PO daily, increase by 7mg per day at one week intervals to the recommended dose of 28mg PO once daily. Combination: Convert from existing donepezil and memantine dose up to 28mg-10mg PO QD.	Memantine: 20mg per day Namenda XR: 28mg per day Namzaric: 28mg memantine/ 10mg donepezil combination

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	Indication	Dosing Regimen	Maximum Dose
Donepezil (Aricept, Aricept ODT)	Alzheimer's Dementia	5mg PO QHS to start, may increase to 10mg after a minimum of 4 weeks. For moderate-severe dementia, may increase to 23mg per day after 3 months at a daily dose of 10mg.	Mild-Moderate Alzheimer's: 10mg Moderate-Severe Alzheimer's: 23mg
Rivastigmine (Exelon, Exelon Patch)	Alzheimer's Dementia	Oral: 1.5 mg PO BID initially. With a minimum of 2 weeks between dose adjustments, increase	Oral: 12mg per day Transdermal: 13.3mg/24 hour

		dose in increments of 1.5 mg as tolerated (i.e. 1.5 mg to 3 mg BID, 3 to 4.5 mg BID, and 4.5 mg to 6 mg BID) Transdermal: Apply 4.6 mg/24 hr patch topically QD, may titrate dose after a minimum of 4 weeks and good tolerability to 9.5 mg/ 24 hr patch topically QD for as long as a therapeutic effect is maintained; may increase to maximum effective dose of 13.3 mg/ 24 hr topically QD.	
Rivastigmine (Exelon, Exelon Patch)	Parkinson's Dementia	Oral: 1.5 mg PO BID initially. With a minimum of 4 weeks between dose adjustments, increase dose in increments of 1.5 mg as tolerated (i.e. 1.5 mg to 3 mg BID, 3 to 4.5 mg BID, and 4.5 mg to 6 mg BID) Transdermal: Apply 4.6 mg/24 hr patch topically QD, may titrate dose after a minimum of 4 weeks and good tolerability to 9.5 mg/ 24 hr patch topically	Oral: 12mg per day Transdermal: 13.3mg/24 hr

		QD for as long as a therapeutic effect is maintained; may increase to maximum effective dose of 13.3 mg/ 24 hr topically QD.	
Galantamine (Razadyne, Razadyne ER)	Alzheimer's Dementia	IR Tablet: 4mg PO BID then titrate as tolerated with a minimum of 4 weeks between dose increases to 8mg PO BID and 12mg PO BID ER Tablet: 8mg PO QD for a minimum of 4 weeks. Then increase to 16mg PO QD. May increase to 24mg PO QD after a minimum of 4 weeks at 16mg/day. Should be taken in the morning with a meal.	24mg per day

VI. Product Availability

Drug	Availability
Donepezil (Aricept, Aricept ODT)	Tablet: 5mg, 10mg, 23mg Oral Disintegrating Tablet: 5mg, 10mg
Galantamine (Razadyne, Razadyne ER)	Tablet: 4mg, 8mg, 12mg ER Capsule: 8mg, 16mg, 24mg Solution: 4mg/ml
Rivastigmine (Exelon, Exelon Patch)	Capsule: 1.5mg, 3mg, 4.5mg, 6mg Transdermal Patch, ER: 4.6mg/24 hr, 9.5mg/24hr, 13.3mg/24hr Solution: 2mg/ml

VII. References

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CLINICAL POLICY
Acetylcholinesterase Inhibitors

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Minor changes to verbiage and grammar. References updated. Aricept added to criteria.	06.02.17	11.17
Deleted MMSE requirement for Alzheimer's Dementia; Added maximum dose for Parkinson diagnosis: 12mg per day for rivastigmine or 23mg for donepezil.	03.14.19	04.19
1Q 2020 annual review; change criteria to direct to generic donepezil and generic galantamine prior to trial of extended formulations in line with Corporate criteria. Updated numbering from AZ.CP.PHAR.26 to AZ.CP.PHAR.1018.	01.2020	01.2020
1Q 2021 annual review: no significant changes; references reviewed and updated	01.26.21	01.21
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21
1Q 2022 annual review. No significant changes; references reviewed and updated.	1.24.22	01.22

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.