

Changes to PharmaCare Coverage for Cholinesterase Inhibitors

The Alzheimer's Drug Therapy Initiative (ADTI) was started in 2007 to gather evidence on the efficacy, safety and cost-effectiveness of cholinesterase inhibitors (ChEIs) for the treatment of mild to moderate Alzheimer's disease (AD). The ADTI also provided temporary coverage of ChEIs through Special Authority.

The ADTI has now concluded and a final PharmaCare coverage decision has been made.

Summary

- Effective **April 1, 2016**, donepezil is available as a Limited Coverage benefit for patients with mild to moderate Alzheimer's disease who meet the Special Authority criteria.
- Patients who are intolerant to donepezil may be eligible to receive PharmaCare coverage for oral rivastigmine or galantamine through Special Authority.
- PharmaCare coverage is not available for switching ChEIs due to lack of effectiveness as there is insufficient evidence of therapeutic benefit of one ChEI over another.
- Patients should be reassessed on a regular basis to ensure continued therapeutic benefit. A renewal request for the ChEI must be submitted to Special Authority 6 months after initiation of therapy and every year thereafter for patients to receive continued PharmaCare coverage of a ChEI.
- The rivastigmine patch is not an eligible PharmaCare benefit.
- Patients with existing coverage of a ChEI through the ADTI, including the rivastigmine patch, are automatically approved for continued coverage for their current cholinesterase inhibitor.

What did the Ministry of Health consider in making a decision regarding cholinesterase inhibitors?

Please visit www.gov.bc.ca/pharmacareprescribers for the link to detailed information on the reports considered by the Ministry of Health, including the ADTI research studies. A [summary of the ADTI research studies](#) is available at the end of this document.

- A meta-analysis and systematic review evaluated the effect of ChEIs on patient outcomes in patients with mild to moderate Alzheimer's disease. Following is a summary of the review and its findings:
- The 2014 ADTI Clinical Evidence Review included the following:
 - a systematic literature review of randomized controlled trials (RCTs) published between March 1, 2010 and December 31, 2013 evaluating the clinical efficacy and safety of selected ChEIs (to supplement a previously published meta-analysis);
 - a separate literature review of studies (RCTs and observational studies) evaluating quality of life, health care resource utilization, and cost effectiveness; and

- an indirect comparison (network meta-analysis) to estimate the efficacy and safety of the ChEIs relative to each other, including an assessment of various outcomes for rivastigmine patches compared to oral capsules. Thirteen RCTs evaluating donepezil, galantamine, or rivastigmine versus placebo met the inclusion criteria.
- In 2015, an updated literature search of studies published between March 1, 2010 and June 1, 2015 was conducted. The 2015 update did not identify any new studies that qualified for inclusion in the meta-analysis and the results from the updated report were consistent with the findings of the original 2014 ADTI Clinical Evidence Review.
 - The ChEIs demonstrated statistically significant improvements (compared to placebo) in cognitive function, clinical global impression, activities of daily living, and behaviour; however, the clinical magnitude of these differences is small for most outcome measures. For example, the estimated number of patients that need to be treated with a ChEI to achieve a benefit in cognitive function that exceeds the Minimal Clinically Important Difference (MCID) was 7 for donepezil, 7 for rivastigmine and 10 for galantamine. In other words, one patient per 7 patients treated with donepezil will achieve a clinically important improvement due to the drug therapy.
 - No significant differences in clinical benefit and/or safety were found between the three ChEIs. There was insufficient evidence of therapeutic benefit when switching to a different ChEI if a patient experiences clinical ineffectiveness on one ChEI.
 - Odds ratios of withdrawal due to adverse effects at 24 weeks for each ChEI relative to placebo were as follows: 1.48 for donepezil (95% CI, 0.93 to 2.38); 1.95 (95% CI, 1.31 to 2.89) for galantamine; and 2.91 (95% CI, 1.50 to 5.66) for rivastigmine.
- As part of the Ministry's drug review process, the Drug Benefit Council (DBC) considered all of the considerations above and recommended that donepezil tablets be listed as a first-line Limited Coverage benefit, while galantamine capsules and rivastigmine capsules be listed as second-line Limited Coverage benefits for patients who are unable to tolerate donepezil. The DBC also recommended continued coverage for patients who are currently receiving Special Authority coverage for galantamine and rivastigmine capsules and not to list rivastigmine patches at the current price. In making their recommendations, the DBC also considered input from physicians, patients, caregivers, patient groups, and manufacturers, as well as a Budget Impact Assessment and utilization review showing a relatively high drug discontinuation rate for all drugs (i.e., 32-43 percent in year 1, 50-62 percent by year 2, and 64-75 percent by year 3). The rates of discontinuation for rivastigmine (oral or patch) were generally higher than for galantamine and donepezil.
- The [Ontario Drug Policy Research Network \(ODPRN\)](#) conducted a drug class review of the ChEIs and recommended that oral ChEIs be listed as Limited Use benefits for patients with mild to moderate Alzheimer's disease in Ontario. The ODPRN also recommended exploring the option of listing the rivastigmine patch if an appropriate price reduction was achieved and recommended against listing memantine.

How is PharmaCare coverage changing?

Effective April 1, 2016, PharmaCare is covering donepezil as a Limited Coverage benefit through Special Authority according to the criteria below. Coverage is subject to the rules of the patient's PharmaCare plan, including any annual deductible requirement.

For new patients

PharmaCare covers donepezil as a first-line Limited Coverage benefit for eligible patients with mild to moderate Alzheimer's disease. Coverage is available for patients who meet the following criteria:

For the treatment of mild to moderate Alzheimer's disease, Alzheimer's disease with a vascular component, Alzheimer's disease with Parkinsonian features (Lewy bodies), or mixed dementia with Alzheimer's disease, in patients with:

- a [Standardized Mini Mental State Examination \(SMMSE\)](#) score of ≥ 10 to ≤ 26 **AND**
- a [Global Deterioration Scale \(GDS\)](#) stage of ≥ 4 to ≤ 6 .

Approval Period:

Initial: 6 months

Renewals: 1 year

How often should my patient be reassessed?

Patients should be reassessed on a regular basis to ensure continued therapeutic benefit and drug tolerance. Prescribers must submit a renewal request to Special Authority 6 months after initiation of therapy and on an annual basis thereafter for patients to receive continued PharmaCare coverage of a ChEI.

Clinicians should consider discontinuing treatment with a ChEI if a patient experiences clinical ineffectiveness/failure or substantial intolerance to the drug therapy.

For additional information on monitoring and reassessment of ChEI therapy, please refer to [BC Guidelines on Cognitive Impairment](#).

What if my patient is intolerant to donepezil?

If your patient is unable to tolerate donepezil, submit a Special Authority request for coverage of oral rivastigmine tablets or galantamine capsules. Requests for rivastigmine patch will not be considered.

What if donepezil does not work for my patient (clinical ineffectiveness or failure)?

PharmaCare coverage is not available for patients switching from one ChEI to another due to clinical ineffectiveness or failure, because there is insufficient evidence that switching to a different ChEI will provide a better therapeutic effect.

Why is the rivastigmine patch not covered by PharmaCare?

The rivastigmine (Exelon®) patch is not eligible for PharmaCare coverage. In patients with mild to moderate Alzheimer's disease, no statistical differences in efficacy between rivastigmine patches and capsules were reported. Relative to rivastigmine capsule, low dose patches were reported to have fewer nausea, vomiting, weight loss, dizziness, decreased appetite, and headache events, but higher rates of diarrhea. High dose patches and capsules demonstrated higher rates of adverse events as compared to low dose patches. Based on clinical and pharmaco-economic considerations, the rivastigmine patch is not cost effective and does not offer value for money. To address this, the Ministry and the manufacturer of the rivastigmine patch engaged in cost negotiations and but were unable to reach agreeable terms for the patch to become a covered benefit for new patients. The Ministry's decision to not list the rivastigmine patch as an eligible PharmaCare benefit is consistent with the recommendations of the DBC and aligns with the coverage status of other public drug plans in most other jurisdictions in Canada.

For existing patients who already have coverage of a ChEI through the ADTI

Patients with existing coverage through the ADTI for galantamine capsules, rivastigmine capsules or rivastigmine patch are automatically approved for continued coverage. Prescribers must reassess the patient on a regular basis and submit a renewal request to Special Authority every year to obtain continued PharmaCare coverage for the ChEI.

How much do ChEIs cost?

Drug	Dose	Cost per 30 days	Cost per year
Donepezil tablet (Aricept®, generics)	5 to 10 mg PO once daily in the morning	\$27	\$325
Galantamine capsule (Reminyl® ER, generics)	16 to 24 mg PO once daily in the morning	\$37	\$452
Rivastigmine capsule (Exelon®, generics)	3 to 6 mg PO bid	\$42	\$513
Rivastigmine patch (Exelon® patch)	4.6 mg to 9.5 mg per 24 hours	\$147	\$1,791

As all ChEIs have a similar efficacy and safety profile, PharmaCare supports the use of the most cost-effective option (donepezil).

Note: Refer to product monographs for complete dosing information (including dose titrations).

Switching from galantamine or rivastigmine to donepezil

Stop galantamine or rivastigmine and allow a washout period of 2 days before starting donepezil. Start donepezil using the same titration as new starts.

Switching from donepezil to galantamine or rivastigmine

Stop donepezil and allow a washout period of 5 to 7 days before starting either galantamine or rivastigmine. Start galantamine or rivastigmine using the same titration as new starts.

Summary of ADTI Research Studies

- As part of the ADTI, the University of Victoria completed four research studies:
 - The **Seniors' Medication Study** showed that Standardized Mini-Mental State Examination (SMMSE) scores submitted by physicians on Special Authority request forms correlated well with the clock-drawing test and telephone interview for cognitive status.
 - The **Clinical Epidemiology Project** found that the average change in SMMSE score was +1.6 points (out of 30) in ChEI-naïve patients at 6 months; this was consistent with observations in RCTs and was considered to be a small change compared to natural fluctuations between the first and second SMMSE in individual patients. There were no differences in outcomes for the different ChEIs.
 - The **Utilization and Cost Project** reported no change in utilization trends or cost of health services after the introduction of the ADTI, except for a shift in drug costs from other payers to PharmaCare and a small increase in general practitioner services of \$3.70 per patient. The project identified an increase in mortality rates from month to month in ChEI users during the 7 years following diagnosis as compared to a slow decline in ChEI non-users; however, these results are non-conclusive and causation cannot be determined without additional research.
 - The **Caregiver Appraisal Study** concluded that caregivers found that although patients were calmer and disease progression was slowed, minimal improvement in abilities or behavior was observed. The perceived benefit was small and inconsistent. Caregivers' assessments of patients' improvement or deterioration did not correlate well with the clinicians' evaluations on the SA request forms.
 - The researchers concluded that there was insufficient evidence to support coverage of the ChEIs on the basis of these research studies alone.
- As part of the ADTI, the University of British Columbia completed one research study:
 - The **Clinical Meaningfulness in Alzheimer Disease Treatment (CLIMAT) Study** compared two research tools (Overall Patient Assessment Rating [OPAR] scale and the CLIMAT scale) in measuring the treatment outcomes from the ChEIs. The CLIMAT scale was more comprehensive in measuring symptom changes, but the researchers also noted that CLIMAT and OPAR are used in the research setting rather than in clinical practice.