

# **Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation**

## **FINAL**

### **Cholinesterase Inhibitor Drugs (Donepezil, Galantamine, and Rivastigmine) For The Treatment Of Mild To Moderate Alzheimer's Disease Pfizer Canada Inc., Janssen Inc., Novartis Pharmaceuticals Inc., Various Generic Manufacturers**

#### **Description:**

The Ministry of Health is conducting a review of the following through its usual drug review process, including information from the Alzheimer's Drug Therapy Initiative (ADTI):

**Cholinesterase inhibitor drugs (ChEIs) donepezil (Aricept® and generics), galantamine (Reminyl® and generics) and rivastigmine (Exelon® and generics)** for the following Health Canada approved indication:

For the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type.

The ADTI began in 2007 as a "coverage with evidence development" initiative to address a knowledge gap and generate evidence on the effectiveness, safety, cost-effectiveness, and appropriate use of the ChEIs. In addition to the research and education components, temporary PharmaCare coverage of the ChEIs was provided through the ADTI.

Specific PharmaCare coverage policy questions were provided as guidance to the DBC (please refer to Appendix 1). In their review, the DBC considered the following inputs: a meta-analysis of the published literature on the efficacy and safety of ChEIs in mild to moderate Alzheimer's disease (AD) with a systemic review of quality of life, cost effectiveness and dose delivery preference; a pharmacoeconomic review of the cost-effectiveness of the ChEIs; the Final Recommendation for rivastigmine patch (Exelon®), completed by the Common Drug Review (CDR) on July 23, 2008, which included clinical and pharmacoeconomic evidence review material and the recommendation from the Canadian Drug Expert Committee (CDEC); a drug class review from the Ontario Drug Policy Research Network (ODPRN) of cognitive enhancers for the treatment of AD; the ADTI research report, containing four University of Victoria studies and comments to inform policy in British Columbia (the Seniors' Medication Study, the Clinical Epidemiological Project, the Utilization and Cost Project, and the Caregiver

Appraisal Study); a BC Health Authorities Review of the ChEIs; and a summary of coverage for ChEIs by Canadian jurisdictions.

Researchers from the University of Victoria gave a presentation about the ADTI studies to the DBC and were available to answer questions at the meeting.

The DBC also considered Patient Input Questionnaire responses from 38 Patients, 356 Caregivers, and 2 Patient Groups (the Alzheimer Society of BC, the Lutheran Senior Citizens Housing Society - Zion Park Manor), Clinical Practice Reviews from two specialists and one general physician, Manufacturer comments from Pfizer Canada Inc., Janssen Inc., and Novartis Pharmaceuticals Inc., as well as a Budget Impact Assessment.

### **Dosage Forms:**

- Donepezil (Aricept® and generics) is available as 5 mg and 10 mg tablets and 5 mg and 10 mg rapid dissolving tablets.
- Galantamine (Reminyl® and generics) is available as 8 mg, 16 mg and 24 mg extended release capsules.
- Rivastigmine (Exelon® and generics) is available as 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules; 2 mg/ml solution; and 4.6 mg/24 hours and 9.5 mg/24 hours patches.

### **Recommendations:**

1. **Overall Coverage Recommendation:** Based on the evidence provided, the Drug Benefit Council (DBC) recommends that the cholinesterase inhibitor drugs (donepezil, galantamine, and rivastigmine) should be listed for the treatment of mild to moderate Alzheimer's Disease in the following manner:
2. **Drug-Specific Coverage Recommendation:** The DBC recommends that the cholinesterase inhibitor drugs for the treatment of mild to moderate Alzheimer's Disease should be listed as follows:
  - Donepezil tablets should be listed as a Limited Coverage benefit with Special Authority criteria, given that there are no significant differences between the cholinesterase inhibitors and the most cost-effective product should be prioritized;
  - Galantamine extended release capsules and rivastigmine capsules should be listed as second-line Special Authority benefits only for patients experiencing intolerance to donepezil;
  - Patients switching cholinesterase inhibitors due to ineffectiveness (clinical failure) should not be covered;

- Patients who are currently receiving Special Authority coverage for galantamine and rivastigmine capsules through the ADTI should have their coverage of these drugs continued (i.e., “grandfathered”);
  - Do not list rivastigmine patches at the current price;
  - Do not list donepezil rapid dissolving tablets or rivastigmine oral solution.
3. **Initial Criteria:** The DBC recommends that the Special Authority criteria for initiation of donepezil coverage be similar to the criteria used in the Alzheimer’s Drug Therapy Initiative (ADTI). The criteria for galantamine and rivastigmine should include intolerance to donepezil. The DBC did not identify any subpopulations that would demonstrate a particular response to the cholinesterase inhibitor drugs.
  4. **Renewal Criteria:** The DBC recommends that the Special Authority criteria for renewal of cholinesterase inhibitor coverage be similar to the criteria used in the Alzheimer’s Drug Therapy Initiative (ADTI). The criteria for galantamine and rivastigmine should include intolerance to donepezil. The DBC did not identify any subpopulations that would demonstrate a particular response to the cholinesterase inhibitor drugs. The recommended duration of coverage should be 6 months.
  5. **Long-Term Institutional Care Setting:** Based on the evidence provided, the DBC recommends that permanent residents of licensed residential care facilities (PharmaCare Plan B patients) should receive coverage of the cholinesterase inhibitor drugs using the same criteria as above.

### **Reasons for the Recommendation:**

#### **1. Summary:**

- The three ChEIs provide statistically significant improvements in cognitive function, clinical global impression, activities of daily living, and behavior versus placebo.
- Although the improvements in outcome measures with the ChEIs are statistically significant, they do not reach the minimal clinically important difference (MCID) for most measures.
- There do not appear to be significant differences in efficacy or safety between the three ChEIs.
- Cost-effectiveness analyses indicate there are small differences in costs and quality of life (QoL) between the three ChEIs.
- At current prices, the annual cost of ChEI therapy is lowest with donepezil (\$380 per patient per year) and highest with the patch (\$1,774 per patient per year) and 2 mg/mL solution forms of rivastigmine.

- Due to the substantially similar efficacy and safety among the three ChEIs, the choice of drug and product can primarily be based upon the cost of therapy.
- There is no evidence of therapeutic benefit from a different ChEI if a patient experiences ineffectiveness (clinical failure) from a first ChEI.
- The criteria used in the ADTI are reasonable, and ongoing coverage should be assessed using a validated and structured tool to measure effectiveness at a reasonable interval.

## 2. Clinical Efficacy

- The DBC also considered a meta-analysis of efficacy and safety of the ChEIs in mild to moderate Alzheimer's disease, which evaluated the effect on patient outcomes compared with placebo and to each other in patients with mild to moderate stages of Alzheimer's disease. The meta-analysis and its update, which includes studies up to June 1, 2015, found that overall, there were statistical benefits in efficacy with an offsetting increased risk of tolerability of all three drugs versus placebo, but the clinical benefit is small and may not be clinically meaningful.
- The August 2015 Ontario Drug Policy Research Network (ODPRN) Final Consolidated Report on Cognitive Enhancers for the Treatment of Alzheimer's Disease found that the three ChEIs were effective improving cognition for patients with mild to moderate AD. Donepezil was the only drug that helped improve cognition for severe patients. Although the drugs were found to statistically significantly improve cognition, the improvement was minimal for most patients. None of the drugs were helpful in improving functionality or behaviour.
- Although the differences between the drugs and placebo were statistically significant, they did not reach the MCID for most measures.
- The DBC also considered the ADTI research report, which contained four University of Victoria studies and comments.
- The Seniors' Medication Study (SMS) was a prospective longitudinal observational study that sought to understand outcomes of cholinesterase inhibitor (ChEI) patients with an initial indeterminate response and to assess the adequacy of the Standardized Mini-Mental State Examination (SMMSE) on the Special Authority (SA) forms used by the ADTI. The SMS revealed SMMSE scores submitted by physicians on Special Authority forms (SA) correlated well with the Clock-Drawing Test (CDT) and Telephone Interview for Cognitive Status (TICS). A positive effect was noted for some patients but the data did not reveal which patients.
- The Clinical Epidemiological Project (Clin Epi) observational study drew on data from SA and provincial administrative datasets in order to examine response to ChEIs among those covered under the ADTI. SMMSE scores and other cognitive function measures fluctuated considerably between enrolment and first SA renewal, even among 'non-naïve' patients. SMMSE response could not be predicted from available data nor were there differences in outcomes for different types of ChEIs. There was indirect evidence that a drop in SA-measured cognitive function was associated with early stopping of ChEIs. The findings were limited by lack of a valid comparison group, large loss to follow-up, and many 'stoppers' (patients no longer covered by ADTI but still taking the medication).

- The Utilization and Cost Project is described further under “Economic Considerations.”
- The findings of the Caregiver Appraisal Study (CAS) of caregiver perceptions of the effects of ChEIs suggest that some families see some benefit but the benefit is neither overwhelming nor consistent. If a placebo effect is assumed, the perceived effectiveness is underwhelming. Caregivers’ appraisals of patients’ improvement or deterioration did not correlate well with clinician assessments on SA forms.

### **3. Safety**

- All ChEIs cause more gastrointestinal adverse effects compared to placebo, although the rivastigmine patch caused fewer gastrointestinal effects than oral ChEIs. Rivastigmine low dose patches, relative to the capsule form, had fewer adverse events for nausea, vomiting, weight loss, dizziness, decreased appetite, and headaches but higher rates of diarrhea.
- The DBC discussed the safety signal observed in the ADTI research studies, relating to an increased rate of mortality and faster time to institutionalization among patients taking ChEIs. The researchers emphasized that this observation is only hypothesis-generating, and the DBC also questioned the validity of this result given the potential for bias and confounding in an uncontrolled, observational trial.

### **4. Economic Considerations**

- The meta-analyses of the safety and efficacy of the three ChEIs, which also included cost-effectiveness analyses, indicated there are small differences in the costs and quality of life (QoL) between the three drugs.
- The August 2015 ODPRN Final Consolidated Report found that donepezil was the most cost-effective monotherapy. The Ontario report recommended that a reduction in price of the rivastigmine patch 55% would be cost-effective.
- At current prices, the DBC found that rivastigmine patch would not be recommended, considering costs relative to benefits.
- The Utilization and Cost Project (U & C) found that the ADTI policy was not associated with a change in patterns of health care utilization and cost, except for a shift in costs from other payers to PharmaCare and a small increase in costs of visits to general practitioners, likely reflecting fees associated with the ADTI or additional visits for SA renewals.

### **5. Of Note**

- Clinical Practice Reviews from one general practitioner and two specialists noted that the ChEIs appear to improve cognition some patients with mild to moderate AD, but not severe AD, and that patients experiencing intolerance (particularly GI intolerance) should have the option of coverage with the other drugs or the rivastigmine patch.

- Patient Input Questionnaire responses from 38 Patients, 356 Caregivers, and 2 Patient Groups (the Alzheimer Society of BC and the Lutheran Senior Citizens Housing Society - Zion Park Manor) provided useful information, especially regarding the difficulty in providing care for AD patients. Many caregivers reported that the ChEI drugs slowed the progression of AD and restored some cognitive functions in patients under their care. Caregivers expressed a need for drugs that will allow AD patients to retain their independence and allow their caregivers to work full time. A majority of caregivers felt the ChEIs were easy to use and tolerable, although donepezil was most mentioned for side effects.

*Appendix 1: PharmaCare Coverage Policy Questions for Consideration*

1. **Overall Coverage Recommendation:** Based on the evidence provided, should the British Columbia Ministry of Health (the Ministry) provide PharmaCare coverage of the cholinesterase inhibitor drugs (donepezil, galantamine, and rivastigmine) for the treatment of mild to moderate Alzheimer's Disease? Please explain.
2. **Drug-Specific Coverage Recommendation:** Among the cholinesterase inhibitor drugs, does one or more demonstrate greater therapeutic benefit (efficacy, effectiveness, or safety), and if so, how should these be prioritized for PharmaCare coverage?

If there are no significant differences, should the most cost-effective drug/product be chosen for coverage? Generics are now available for oral products containing donepezil, galantamine, and rivastigmine (subject to the PharmaCare Low Cost Alternative policy).

There is currently no generic available for the rivastigmine transdermal patch. Based on the evidence provided, should rivastigmine patch be a covered option? And if so, should the patch product be covered similar to or tiered behind oral rivastigmine (e.g., option for the patch to be subject to the Low Cost Alternative policy and/or additional Limited Coverage criteria)?

3. **Initial Criteria:** Are there subpopulation(s) that demonstrate a particular response to the cholinesterase inhibitor drugs, and if so, should they be included or excluded for initial coverage? If one or more of the cholinesterase inhibitor drugs are recommended for PharmaCare coverage, should the initial criteria be the same as the ADTI criteria, or modified?
4. **Renewal Criteria:** Are there subpopulation(s) that demonstrate a particular response to the cholinesterase inhibitor drugs, and if so, should they be included or excluded for ongoing coverage? If one or more of the cholinesterase inhibitor drugs are recommended for PharmaCare coverage, should the renewal criteria be the same as the ADTI criteria, or modified? What is the recommended duration of coverage (i.e., when should a renewal be assessed)?
5. **Long-Term Institutional Care Setting:** Based on the evidence provided, should the Ministry provide PharmaCare coverage of the cholinesterase inhibitor drugs in the long-term institutional care setting? If yes, which drugs should be covered and should the coverage criteria be different in the community care setting? If not, please explain.