Manufacturer Comments – Clinical Evidence Review Report and Supplemental Update and Pharmacoeconomic Review Report

Drug Product Generic name (Brand name)	**Alzheimer's Drug Therapy Initiative** donepezil (Aricept)
Manufacturer (Distributor if applicable)	**Pfizer Canada Inc.**

Background: To support the Ministry's commitment for increased transparency in its drug review process, the Manufacturer is asked to provide objective comments on the Clinical Evidence Review Report and the Supplemental Update, the Pharmacoeconomic Review Report and the ADTI Research Report. The Manufacturer comments on these reports will be forwarded to the Drug Benefit Council, who will then consider them when making their recommendations to the Ministry. Please note that comments from the Manufacturer may be posted on the PharmaCare website as part of the Ministry's commitment for increased transparency.

Manufacturer Input Guidance:

- **Please indicate whether there is agreement or disagreement with the reviewers reports. All comments should be evidence-based and referenced.**

- **This forum is not intended as an opportunity for the Manufacturer to introduce new clinical evidence. New clinical evidence included in Manufacturer comments will not be considered by the DBC. If the manufacturer would like new clinical evidence considered by the DBC, the Manufacturer will need to resubmit through the drug submission process.**
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(Length: up to 4 pages in total, including appendices)

PFIZER RESPONSE BEGINS NEXT PAGE

RESPONSE FROM PFIZER

Background

Alzheimer's disease (AD) is a horrifying degenerative condition that robs its victims of their most precious memories and long-term cognitive functions. It is a major source of impairment for afflicted patients and their families, as well as a major financial burden for health systems, such as British Columbia's. Although the researched based life sciences and pharmaceutical industry has invested and continues to devote hundreds of millions of dollars towards researching this complex and frustrating disease, we have yet to find a cure. However, significant advances have been realized, including cholinesterase inhibitors (ChEI), a class of drugs that can help those most by improving their quality of life.

In 1997, Health Canada approved the first ChEI treatment for Alzheimer's disease, donepezil (ARICEPT). This was followed by the approval of rivastigmine (EXELON) in 1999 and galantamine (REMINYL) in 2000. Between 2000 and 2003 Canadian provinces approved public coverage for ChEIs with criteria. British Columbia did not provide coverage.

In 2003, a conference attended by more than 50 British Columbia physicians (family physicians, psychiatrists, neurologists, and geriatricians) was convened to review all the available published randomized controlled trials for all the ChEIs. Data from each trial were presented in order to evaluate the efficacy of the drugs as well as to assess the level of evidence available to support treatment for AD patients in the community. Specifically, the British Columbia family and specialist physicians looked at the efficacy of ChEIs on the symptoms of Alzheimer disease, including effects on cognition, function, and behaviour. They also assessed the evidence pertaining to the overall impact these medications had on global function, caregiver burden and pharmacoeconomics. The conclusion reached at this conference was that ChEIs have a positive effect on mild to moderate AD patients "and that these medications should be offered to all those without contraindications as a standard of care".[1]

In 2007, the Government of British Columbia announced a 3 year coverage with evidence study (the Alzheimer's Drug Therapy Initiative) that would provide coverage for an expected 25,000 patients in a joint partnership with the manufacturers of the ChEIs. The study was budgeted for $78 million with approximately $ 8 million being supported by the pharmaceutical industry. Pfizer, along will the other two manufacturers, participated in the ADTI by providing financial support for drug costs to patients in the first 90 days of treatment who were deemed by their physician an "non responders". This unique partnership with industry was designed as a solution-oriented model so that only those demonstrating value from therapy would be part of the publicly funded program. Although the industry also provided one-time educational grants at the launch of the ADTI, they had no role in the research component of the study lead by principle investigators at the University of Victoria.

[1] Beattie BL, Feldman H. Treatment Efficacy in Alzheimer Disease (TREAD) conference. BC Medical Journal vol. 46 no.7 September 2004 pp 344-347

In 2010, the Ministry of Health approached the industry partners to extend their financial contribution to the ADTI due to the fact there were insufficient numbers of patients enrolled in the research component of the study. To ensure the successful conclusion of the ADTI, Pfizer and the other two industry partners extended their commitment in 2010 and again in 2012.

ADTI

In August 2015, Pfizer received the ADTI study results from the Ministry of Health and asked to respond to its findings. Unfortunately, the time allocated by the Ministry for review does not allow for Pfizer to provide comprehensive and thorough objective comments. With more time and un-embargoed access to the research study it would be our intention to investigate further into the four study arms. Examples of the questions we have are:

- With respect to the Seniors' Medication Study (SMS), is the N=224 a reasonable number on which to base a prospective observational longitudinal study?
- With respect to the Clinical Epidemiological Project (Clin Epi), were there issues with data and SA compliance limit the ability to satisfactorily answer the research question outlined in the study deliverable?
- With respect to the Utilization and Cost Project (U&C), the drug cost data analyzed used the period between 2004 and 2011. Did their analysis include the financial cost offsets provided by the manufacturers throughout the course of the study (2007 – 2014)? Also, drug costs were reduced starting in 2012 due to generic pricing. Would the U & C conclusions be different if investigators had used up to date drug cost information? There is also reference to interviews with 22 individuals in order to understand cost effectiveness but the details of these interviews were not found.
- With respect to the Caregiver Appraisal Study (CAS), the objective was to use a random sample of caregivers but the investigators acknowledge that the sample analyzed is not representative. Given the issues related to recruitment can the findings in the CAS be generalized to learn about family caregivers' perceptions?

ARICEPT

ARICEPT (donepezil hydrochloride) is approved by Health Canada and is indicated for the symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type. The scientific efficacy of ARICEPT in patients with mild to moderate Alzheimer's disease was established in two 24 week and one 54 week placebo-controlled trials. Efficacy in patients with severe Alzheimer's disease was established in two 24 week/6month placebo-controlled trials.[2]

ARICEPT's extensive clinical trial dossier includes three Phase 3 trials in patients with mild to moderate Alzheimer's Disease, one Phase 3b trial in patients with moderate to severe Alzheimer's disease, three Phase 3 trials in patients with severe Alzheimer's disease, and three Phase 3 trials in patients with mild to moderate vascular dementia.

[2] ARICEPT/ARICEPT RDT (donepezil hydrochloride) Product Monograph

ODPRN

The Ontario Drug Policy Research Network (ODPRN) recently conducted a drug class review on the effectiveness, safety and accessibility of cognitive enhancers such as ChEIs using multiple research methods. The ODPRN review included a qualitative study to determine the experiences of use and prescribing; a systematic review to determine efficacy and safety (including mortality); a pharmacoepidemiological analysis to determine patterns of use in Ontario and across Canada; an environmental scan to determine national and international guidelines and public coverage models and pharmacoeconomic analyses to determine the cost of public drug funding under different coverage policies.

In making its key considerations for reimbursement options, the ODPRN analyses considered efficacy, safety, tolerability, accessibility, utilization and pharamcoeconomics for ChEIs. It would be a disservice to the report to summarize the findings in this response but this is an important study for the BC Drug Benefit Review Committee to review because it is a Canadian-based research project examining the same medications as those studied in the ADTI, addressing similar research questions asked in the ADTI and published in the same month (August 2015).[3]

Coverage with Evidence

The BC Ministry of Health should be commended for the effort and innovation it took to build a BC-specific Coverage with Evidence reimbursement model for the cholinesterase inhibitor class of drugs in 2007. If it had not been for the ADTI, tens of thousands of British Columbians may never have had public access to these medications, and treatment would only been available to those with private coverage or the means to pay for the medication themselves. The ADTI was the model chosen to help those suffering from this devastating disease that could potentially benefit but could not afford the prescription costs (approximately $5 a day). Pfizer was proud to partner with the Government to help ensure that only those patients demonstrating benefit from the medicine were being covered as beneficiaries through the Medical Benefits Pharmaceutical Services Division.

Moving forward, the Coverage with Evidence approach may be useful in other therapeutic classes. Learning from the ADTI, Pfizer would recommend the following:

- ARICEPT, in addition to being a well-studied medication for efficacy and safety, had been widely prescribed to patients across Canada and around the world in real-life clinical settings for a decade before the ADTI was launched. Coverage with Evidence reimbursement initiatives would be more valuable in drug classes that are new to the market and data in the real-life Canadian setting is not well documented or understood. Or in situations where the drug or class of drugs is not reimbursed in any other jurisdiction but the BC Ministry of Health sees a potential value and unmet need for the people of British Columbia.

[3] One of the final recommendations in the report concluded that donepezil was the most cost-effective monotherapy. Ontario Drug Policy Research Network. Final Consolidated Report, Cognitive Enhancers for the Treatment of Alzheimer's disease, August 2015. www.odprn.ca

- Timelines between the launch and completion of the Coverage with Evidence initiative should be in the 3 to 5 year range. This could include periodic updates on the progress and research findings to the public during the initiative.
- Stakeholder review and participation in the research proposal and review should be encouraged (primary care physicians, patients, specialist physicians, nurses and allied health professionals, caregivers, industry, professional organizations and advocacy groups).

Summary

Originally discovered by the Japanese pharmaceutical firm Eisai and marketed in Canada by Pfizer, donepezil is now available in many generic forms. The ADTI was the last major initiative associated with donepezil for our company and we are proud of our past participation and contribution.

It is our hope that continued and future research will produce an improvement for AD patients, and that the next generation of treatments for Alzheimer's disease will provide a cure to this debilitating disease. Until that hope is realized, the class of drugs known as cholinesterase inhibitors are the best available standard of care. ARICEPT (donepezil) is well researched, safe and affordable. And most importantly, for many donepezil (and the other ChEIs) provide improvement in cognition and ameliorate the symptoms associated with the relentless and inexorable deterioration of the disease.

Pfizer has no commercial interests in the final decision of the Drug Benefit Committee and the outcome of this review, but for the AD patients and their families, we respectfully ask that the Ministry of Health continue to provide these medicines as a publicly funded pharmaceutical benefit and maintain the advantages gained with the ADTI.