

Manufacturer Comments – ADTI Final Report, Clinical Evidence Review Report (and Supplemental Update) and Pharmacoeconomic Review Report

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| Drug Product Generic name (Brand name) | Alzheimer’s Drug Therapy Initiative rivastigmine (PrExelon [®] & PrExelon [®] Patch) |
| Manufacturer (Distributor if applicable) | Novartis Pharmaceuticals Canada Inc. |

On August 20, 2015 Novartis received the Clinical Evidence Review Report (2014) and supplemental update (2015), the Pharmacoeconomic Review Report and the ADTI Final Report prepared by the University of Victoria. Please find below Novartis' comments on these Reports.

The ADTI Report concludes by proposing 3 options (ADTI Final Report, p16-17), namely

1. There is insufficient evidence to support coverage of ChEIs based on the findings from the four ADTI studies.
2. Do a Reduction in Coverage with Evidence Development using a 'designed delay' method.
3. Special Authorisation approvals be maintained in order to obtain valuable data and patient follow-up on a difficult category of patients, but that the SA criteria be modified from those used for the ADTI program.

Novartis would like to comment on each proposed option.

Insufficient evidence to support coverage of ChEIs based on the findings from the four ADTI studies

Novartis disagrees with this statement and inferred implication, i.e. a recommendation not to provide Pharmacare coverage for patients requiring ChEIs in the future. The ADTI studies produced interesting insights into the treatment of AD in BC. The ADTI program also identified areas that would benefit from further research and it proposed methods to potentially fill the information gaps. However, the limitations on the methodology and results that were clearly stated by the Authors throughout the Reports make an evidence-based recommendation on coverage of ChEIs not possible. For example:

Seniors' Medication Study (SMS): *"There is limited understanding about what assessment tools are effective in measuring treatment response for this particular class of drugs and disease initially and over time."* (ADTI Final Report p.20). *"There are a number of research limitations that impact on the generalizability of these findings."* (ADTI Final Report, p.48).

Clinical Epidemiology Project (Clin Epi): *"The key dataset for Clin Epi that contained assessments of patients' cognitive, functional, behavioural, and global responses (the outcome measures of interest for Deliverables 1, 2, and 4) was severely limited by 2 factors that make the conclusions drawn from analyses of this dataset tentative."* (ADTI Final Report p.68). *"Attempts to determine what predicted a positive or negative response to the ChEI were not successful (Deliverables 1e and 2)."* (ADTI Final Report p.70). *"In the absence of a control group, determining the effect of ChEIs on mortality was not possible."* (ADTI Final Report p.71).

Despite limitations identified by the author, the Clin Epi Project concludes *"It appears that a substantial proportion of patients who remain on the ChEI and have their SA renewed score better than expected on the cognitive measures (SMMSE, and positively on the cognitive component of the OPAR measure) and to a lesser extent on the behavioural measure, and furthermore the largest proportion of patients experience the positive response within the first 6 months of their initial SA."* (ADTI Final Report p.73).

Utilization & Cost Project (U&C), on cost-effectiveness of ChEIs: *“Due to limitation of the data and methodology, we were unable to conduct a cost-effectiveness study, but rather examined the effect of ChEI use on clinical outcomes (death, entrance to long-term care) and costs of health services.”* (ADTI Final Report p.15). *“Due to the nature of the data and study design (observational study and patients divided to user groups early) the results are inconclusive; causation cannot be imputed. The findings are informative insofar as they signal a need for caution and further investigation but they do not imply certainty.”* (ADTI Final Report p.15).

Caregiver Appraisal Study (CAS): *“These analyses point to the importance of multiple measures in this area and of not generalizing from one measure to other areas.”* (ADTI Final Report p.111). *“Once again, measurement matters. Overall, physicians and caregivers often disagree on their assessment of the effectiveness of ChEIs.”* (ADTI Final Report p.112)

The insufficient evidence from the four ADTI studies can be compensated by the published scientific evidence supporting the use of ChEIs in AD as a therapeutic intervention. Drugs in the ChEI class included in the ADTI studies were reviewed by Health Canada (and other national Health Authorities) and approved for use in Canadian AD patients based on the submitted scientific evidence demonstrating the efficacy and safety of these agents.

In addition, the Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)¹ support the use of ChEIs. Specifically, *“All three cholinesterase inhibitors have demonstrated efficacy for mild to severe AD. We recommend a trial of a cholinesterase inhibitor for most patients with AD (Grade 1A)”* and *“Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection of which agent to be used will be based on adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.”*

Benefits of ChEIs, including rivastigmine, are also stated in the Reports. For example, the Meta-analysis (MA) Report 2014 (and the 2015 update) highlights the benefits versus placebo *“Overall, the evidence suggest that all of the 3 drugs provide benefit versus placebo in improvement in cognitive function, clinical global impression, activities of daily living, and behaviour”* (MA Report p.12) and that ChEIs can be viewed as a class of drugs *“Two large systematic reviews of the literature have been conducted by NICE and the Cochrane Collaboration. From their respective reports the overall conclusions regarding a comparison of donepezil, rivastigmine and galantamine suggest that that there is insufficient evidence to indicate that one treatment is better than another. The three drugs appear to show similar benefit for cognitive function and global assessment. Therefore it has been suggested that the ChEIs are taken as a class of drugs.”* (MA Report p.7).

The MA Report highlights specific benefits for the rivastigmine patch formulation, where *“One benefit for patches versus oral is a higher level of satisfaction for caregivers. Patch therapy also appears to improve adherence to therapy, to reduce discontinuation rate and improve ease of administration.”* (MA Report p.10). From a cost-effectiveness perspective, the MA Reports indicates that *“There appears to be favourable cost effectiveness for each drug versus placebo, such as cost neutrality or small cost savings and small differences in quality of life. Based on the*

evidence, there is an absence of differences in costs and quality of life between drugs.” (MA Report p.10).

Reduction in Coverage with Evidence Development using the ‘designed delay’ method

Novartis is not in agreement with this option due to the very limited details on the objectives and the implementation of such an option, and the impact that it will have on current or future AD patients, families & caregivers in British Columbia who may benefit from the availability of ChEI treatment as a Pharmacare benefit.

“If the MoH decides to curtail coverage of cholinesterase inhibitors (ChEIs), it would be ethical to do a Reduction in Coverage with Evidence Development using the ‘designed delay’ method previously used by PharmaCare in a restriction of coverage of respiratory medications in 1999. In this instance, impact could be measured by delaying the policy change in some areas and comparing patients’ rates of entry into long-term care between comparable areas.” (ADTI Final Report p.118).

It is unclear by what standards this ethical assessment is based on. The proposal relies upon ‘rate of entry in LTC’ as a key criteria for assessing the benefits of ChEI treatment in AD patients. The rate of entry into Long Term Care is only one of many parameters that should be taken into account when accessing the value of AD treatment with ChEIs.

Without more detail, it is unclear how this ‘designed delay method’ will provide additional evidence to the current ADTI Reports to inform BC Pharmacare decision making on coverage and benefit status of ChEIs. *Curtail* and *restriction of coverage* refer to a reduced access to ChEIs for AD patients. A likely impact of this method would be to prevent some AD patients from receiving timely access to ChEI treatment, which would negatively impact the benefits and value of ChEIs treatment the largest proportion of patients experience a positive response from treatment within the first 6 months of their initial SA (ADTI Final Report p.73).

ChEIs currently have SA benefit status and their use is already limited by the SA criteria (initial coverage, renewal/switching).

SA maintained in order to obtain valuable data and patient follow-up on a difficult category of patients, but that it be modified

Novartis agrees with maintaining SA benefit status and the use of a SA form for ChEIs. We believe that the changes to SA Forms identified in the Final Report are suggestions that would benefit from further assessment by, and consultation with physician users of the forms.

We note that the Final Report has indicated that overall, geriatric specialists saw benefits to the SA and the ADTI Program. These specialists felt the SA improved the amount and type of follow-up with patients covered by SA (ADTI Final Report p.48). The ADTI Final Report Authors saw an

opportunity to improve the SA as physicians were quick to identify issues within the MoH with regards to SA approvals, paper-flow, Ministry staff, billing complexities, and policy development (ADTI Final Report p.47).

Conclusion

Novartis agrees with the Authors that *“these analyses point to the importance of multiple measures in this area and of not generalizing from 1 measure to other areas.”* (ADTI Final Report p.17). ADRD is a syndrome with a constellation of symptoms with a variable mix of underlying pathologies. Realistically therefore, we can expect that there would be a constellation of measurements required to assess change in various aspects of domains most impacted by this disease (ADTI Final Report p.50).

There is a need for a holistic approach to AD treatment, and availability of ChEIs as a therapeutic option is an integral part of the treatment armamentarium. Since it is not possible to identify in advance which AD patients will benefit the most from ChEIs [“Attempts to determine what predicted a positive or negative response to the ChEI were not successful” (ADTI Final Report p.70)], AD patients and clinicians need to have access to individualized treatment options and coverage of ChEIs as provincial drug plan benefits.

Novartis agrees with the third option where SA benefit status is maintained for AD patients in British Columbia. This would ensure that appropriate AD patients and caregivers can benefit from ChEIs treatments, including Exelon® and Exelon® Patch, that clinicians have access to recognized and approved treatment options and that BC Pharmacare achieves value from ChEIs through monitored access (SA form).

Finally, Novartis is committed to maintain its collaboration with the BC government, as we have during the original term of the ADTI program (and its extensions,) to ensure that British Columbians affected by AD (patients, families and caregivers) who need Exelon® or Exelon® Patch will have access to this treatment.

Exelon is a registered trademark

References

1. Gauthier S et al. Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Canadian Geriatrics Journal. 2012; 15: 120-26.