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

Drug Product Generic name (Brand name)	**Alzheimer's Drug Therapy Initiative** galantamine (Reminyl)
Manufacturer (Distributor if applicable)	**Janssen 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)

Response

Janssen appreciates the opportunity to review these reports. Please find below comments pertaining to the Clinical Evidence Review and its supplemental update report.

1) These two reports summarize results of systematic literature reviews including trials published from 01-Mar-2010 to 01-Jun-2015. This research is an extension to the two previous large reviews conducted by NICE (Bond et al. 2012) and the Cochrane Collaboration (Birks 2006). The goal is to answer the important question on whether the differences seen between ChEI agents and placebo are clinically meaningful in the short and long term.

   In both NICE and Cochrane systematic literature reviews, an extensive search of health care and ongoing trial databases were conducted which included MEDLINE, EMBASE, PsycINFO and others. However, the search strategy in the Clinical Evidence Review report indicated that only PubMed was searched. The company strongly believes that this approach is inadequate for a thorough systematic literature review. As a result, the search failed to identify the publication cited below which presents data from an important galantamine trial:

   Hager K, Baseman AS, Nye JS, et al. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. Neuropsychiatr Dis Treat 2014(10):391-401.

In this galantamine trial, 1,024 galantamine- and 1,021 placebo-treated patients received study drug, with mean age ~73 years, and mean (standard deviation [SD]) baseline MMSE score of 19 (4.08). Cognitive impairment, based on the mean (SD) change in MMSE scores from baseline to month 24, significantly worsened in the placebo group (−2.14 [4.34]) compared with the galantamine group (−1.41 [4.05]) (P<0.001). At 24 months, galantamine significantly reduced the decline in cognition in patients with mild to moderate Alzheimer's disease.

Hence, the aforementioned study did demonstrate clinical benefit of galantamine over placebo with respect to cognitive impairment.

2) Despite the many study limitations (pg. 27-28) as stated in the report entitled, "A meta-analysis of efficacy and safety of cholinesterase Inhibitors in mild to moderate Alzheimer's disease with a systemic review of quality of life, cost effectiveness and dose delivery preference", results of the meta-analyses concluded that the clinical benefit of all three ChEIs is small and may not be clinically meaningful.

In section 3.4.6 (page 22) of the Clinical Review report, it states that "….the confidence intervals of any of the drugs do not exceed the MCID for the ADAS-cog, and may not be clinically important. When we estimated the percentage of confidence interval for the mean difference that was greater than the MCID for each study, and then pooled the percentages across the studies, there were detectable improvements versus the MCID. The estimated percentage of patients treated with ChEIs and achieved the Minimal Clinical Important Difference (MCID) on ADAS-cog at 24 weeks was between 25.9% and 32.3% versus 16.6% for placebo patients."

It is not clear from the report whether the above stated percentage difference is statistically significant and how the "detectable improvements" lead to the conclusion that the benefit is small and probably not clinically meaningful.

In reference to section 2.2.7.1 (page 19), it is also not clear in terms of references in support of a MCID for ADAS-cog difference of 4 points. Although it states on page 26 that "….the suggested clinically important difference for ADAS-cog *has been stated by the FDA* to be 4 points, the differences of drugs versus placebo were all 2 to 3 points, and the differences between drugs were 1 point or less" in reference of Rockwood, 2007. This paper does not appear to validate the clinical importance of the of 4-point difference in ADAS-cog/11, rather it starts by proposing that a change of 4 points in ADAD-cog is the MCID and examines how this change compared with measures of clinical meaningfulness in an open-label study.

The document states the limitations of the systematic review and meta-analysis on page 27 that "…another limitation of the meta-analysis is the establishment of the MCID for patients with AD. The MCID has been suggested to be based on the primary outcome of ADAS-cog with a value of 4. It is unclear if this difference applies to patients with mild, moderate or severe AD specifically or to all

AD patients. It is possible that the MCID may have an anchor such that the MCID may be different for different severities of the disease."

Therefore, given there is no clear definition of MCID in AD and a value of 4 is not well established, the company view is that the conclusion stated in the clinical evidence report appears too definitive/strong and we respectfully suggest this be re-evaluated.