

**Post Market Review
Pharmaceutical Benefits Scheme anti-dementia
medicines to treat Alzheimer Disease**

(donepezil, rivastigmine, galantamine and memantine)

Report

to the

Pharmaceutical Benefits Advisory Committee

Plain Language Summary

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Report Prepared by:

Centre for Health Economics, Monash University

University of South Australia

Veterans' Medicines Advice and Therapeutics Education Services

Department of Health and Ageing

Pharmaceutical Policy Branch

RaggAhmed (plain language summary)

Summary

Overview

This is a plain language summary of the report prepared for the Pharmaceutical Benefits Advisory Committee (PBAC) to provide more recent evidence on the effectiveness and cost effectiveness of Pharmaceutical Benefits Scheme (PBS) subsidised cholinesterase inhibitors (CEIs) and memantine for the treatment of AD. This summary has been prepared for circulation to all interested stakeholders prior to PBAC consideration. The full report or specific parts of the report are available on request. Please refer to the PBS website (pbs.gov.au) for further information on the review process and contact details to request parts of the full report.

This report, PBAC sub-committee advice, consumer and sponsor submissions and comments will be considered by PBAC in the near future. Any recommendations from PBAC relating to the PBS listing of these medicines will be provided to the Minister for Health and Ageing for consideration.

The report is comprised of six parts, including:

- the background and context of the review of PBS listed medicines for dementia in AD, and the history of their listing, costs and restrictions
- an overview of current PBS utilisation of cholinesterase inhibitors and memantine in Australia, comparing these results with the patterns of use reported in the Drug Utilisation Sub-Committee (DUSC) Secretariat review (2009), based on a 2004 PBS cohort of initiators to CEIs (Terms of Reference: a)
- an update of the efficacy and safety of CEIs and memantine. A systematic literature review was conducted to determine if any additional evidence on safety and efficacy had been published since the PBS listing of these medicines that could inform PBAC on both short and longer term outcomes (beyond 6 months) when used individually and in combination (Terms of Reference: b)
- a review of the Mini-Mental State Examination (MMSE) as a surrogate for measuring improvement in patients with dementia treated with these medicines; this was addressed by a further search of the literature for published evidence on the validity and reliability of the MMSE tool for detecting clinical changes in dementia related to AD (Terms of Reference: c)

- stakeholder submissions provided to the review as part of the public consultation process (addressing all Terms of Reference)
- a summary of the cost-effective evidence provided when CEIs and memantine were listed on the PBS and the likely impact the current restriction has on limiting utilisation to the intended cost-effective population (Terms of Reference: d).

Part 1 – Background

AD is the most common form of dementia affecting older people. It is a progressive disease that develops slowly but steadily over time. This disease causes irreversible changes to the brain, which impairs memory, understanding and reasoning (cognition).

A number of medicines are subsidised through the Pharmaceutical Benefits Scheme (PBS) for treating dementia in AD. These include the cholinesterase inhibitors (CEIs) donepezil, rivastigmine and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine.

The CEIs work by stopping the breakdown of the chemical acetylcholine in the brain, effectively increasing the level of this chemical. Acetylcholine is used by the nerve cells in the brain and is important for memory. Increasing the level of acetylcholine can increase communication between nerve cells and may improve or stabilise the symptoms of AD.

Memantine acts quite differently to the CEIs. It works by blocking the chemical glutamate. This prevents too much calcium entering the brain's nerve cells, which can damage or affect the function of the cells.

These four medicines do not cure the disease but give some relief from symptoms, and may slow decline in progression of the disease for a period of time in some patients. These medicines also have significant side effects, which means that some people do not tolerate these medicines and need to stop treatment within months of starting.

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the subsidy of these medicines in late 2000. This followed consultation with clinical experts and the pharmaceutical companies that make these medicines. At the time,

PBAC recognised the high clinical need for an effective treatment for people with AD. However the evidence on these drugs was inconclusive and provided little information on how these medicines affected patients' quality of life and on the benefits of treatment, if any, beyond six months. For these reasons, PBAC recommended restricting the subsidy of these medicines beyond six months to only those patients who demonstrated an improvement in their symptoms.

The current PBS restriction allows subsidised CElS and memantine for patients who have a specialist diagnosis of AD and a score of ≥ 10 in the Mini-Mental State Examination (MMSE), a commonly used test of mental function. Continuing treatment beyond six months is restricted to patients who show an improvement of 2 or more points in the MMSE (or equivalent cognitive improvement in the AD Assessment Scale–Cognitive sub-scale [ADAS-Cog]). For those with MMSE scores lower than 10 points due to language or intellectual barriers, access may be sought using the doctor's assessment or clinician's impression scale.

This restriction was put in place by PBAC when these medicines were first recommended for subsidy in 2000 to promote their cost-effective use. However, many carers and clinicians consider there is benefit in continuing treatment with these medicines when there is stabilisation or a perceived slowing of symptom progression, indicating the continuation rule may not always be adhered to in clinical practice.

A review of these medicines listed on the PBS for AD has been conducted as part of a post-market surveillance program to ensure they are being used in a safe and cost-effective way. An initial review of the CElS, conducted by the DUSC of PBAC in 2009, indicated these medicines were being prescribed to more people (approximately 60 per cent of those who initiate treatment) beyond six months than originally expected. This additional use, while not necessarily inappropriate, is not cost-effective use as originally assessed by PBAC.

Part 2 – Current use of cholinesterase inhibitors and memantine

This section of the report addresses the first term of reference for the review.

TOR a): Review recent Australian utilisation data on patient initiation and continuation rates to cholinesterase inhibitors and memantine.

The use of CEIs is increasing and this is expected to continue to grow given the increasing prevalence of the disease in an ageing population in Australia. Over the past five years the total number of PBS prescriptions dispensed increased by 3–4 per cent each year. In 2011 the Australian Government spent over \$60 million dollars on subsidising these medicines, of which approximately 60 per cent was for the drug donepezil, sold under the brand name Aricept®.

The pattern of use of these medicines has not changed much over the past six or seven years. Studies of Australian PBS data found approximately 60 per cent of people who start the treatment continue on it for more than six months. Also, about one-third of people who commence taking these medicines continue taking them for three years or more.

During 2011, 46,183 people received a PBS prescription for a cholinesterase inhibitor or memantine, and of these, 16,651 people (approximately 36 per cent) were new to treatment. However, when these prescriptions were assigned to initiating or continuing restriction codes, 80 per cent of the total number of prescriptions was for patients continuing treatment beyond six months.

Data from the Department of Veterans' Affairs and a 2009 DUSC report showed that between 15–19 per cent of people starting these medicines lived in aged care facilities. These figures are relevant because the main assumption driving the original cost effectiveness assessments of these medicines by PBAC in 2000, and other more recent assessments, is that they can delay time to institutionalisation and reduce health care expenditure. Therefore, the cost effectiveness of using these medicines in a setting where people are already cared for full-time is unknown.

About 30 per cent of people taking CEIs or memantine also use other medicines with sedative and anti-cholinergic effects. These other medicines may have an impact on the initial assessment of a person by affecting the severity of their symptoms. They may also decrease the effectiveness of CEIs when taken together.

The results of this update of the use of PBS-subsidised CEIs and memantine are consistent with the previous findings of the DUSC report in 2009 (based on the 2004 cohort) and later published in LeCouteur et al (2012). That is, there is evidence to suggest that CEIs and memantine are being used in a significant population outside that originally agreed by PBAC as cost effective at the initial listing price.

Part 3 - An update on the safety and efficacy of cholinesterase inhibitors and memantine

This section of the report addresses the second term of reference for the review.

TOR b): Investigate if there is more recent evidence on the safety and efficacy of these medicines that would inform PBAC about their cost effectiveness.

Trials demonstrated that patients given CElS and memantine showed, on average, small improvements in cognitive ability compared with patients given placebo or no drug treatment. The clinical relevance of these improvements measured using assessment scales such as MMSE and ADAS-Cog remains unknown because linking these changes to patient-relevant outcomes such as changes in quality of life has not been demonstrated in clinical trials. The literature search undertaken in this review identified no more convincing evidence reporting improvement in quality of life outcomes or time to institutionalisation compared to those given a placebo.

For patients treated with CElS and memantine, the average change or improvement in cognitive ability was less than that required to continue receiving subsidised treatment beyond six months. The results of trials measuring cognitive response in people given CElS beyond six months were inconsistent. Some studies demonstrated statistically significant differences in people given CElS for one or two years compared with those given placebo, whereas other studies showed that MMSE scores declined at a similar rate to those in the placebo group.

Trials that studied the effect on cognition when these medicines were ceased found that symptoms deteriorated more rapidly than those who stayed on donepezil, galantamine and memantine. No similar trials of the effect of stopping treatment for rivastigmine were found in this literature search.

Observational studies of galantamine have reported delaying death, higher MMSE scores and delayed time to institutionalisation for those treated beyond six months, however the quality of this data is considered to be low when compared to other trials. There is also one small trial that has reported delayed admission to an aged care facility for some patients taking memantine relative to placebo.

This review found there was no difference in behavioural symptoms observed between patients given donepezil, rivastigmine or memantine and those given placebo treatment. There were some improvements in single components of the behavioural assessment tool such as apathy and physical behaviour, however overall

the results from these assessments found no difference between those taking anti-dementia medicines and those taking a placebo. One galantamine trial demonstrated a statistically significant improvement in behavioural symptoms, however five other trials did not.

Review of longer term safety data has not provided any new information on further harms associated with these medicines than previously assessed by PBAC. There are significant reports of side effects such as nausea and diarrhoea, however starting on a low dose and increasing slowly has been shown to help reduce these symptoms.

Taking more than one of the CElS or memantine at the same time appears unlikely to provide any further benefit to patients.

Overall the results of this review of more recent comparative evidence on the effectiveness of CElS and memantine are consistent with previous evidence on safety and efficacy considered by PBAC when the medicines were originally recommended for PBS subsidy.

Part 4 – A review of the Mini-Mental State Examination (MMSE)

This section of the report addresses the third term of reference for the review.

TOR c) Review whether the two-point improvement in Mini-Mental State Examination continues to be an adequate surrogate for measuring improvement in patients with dementia treated with these medicines; and are there other more reliable measures of patient-relevant outcomes?

The MMSE is widely used in clinical practice to assess dementia. It is a short 30-question test that estimates the severity of mental impairment in a person. Factors the MMSE assesses include orientation, short-term memory, attention and calculation, language ability, ability to follow commands, and the ability to perform actions. The MMSE is also used to follow changes in a person's mental capacity over time. The maximum score on the MMSE is 30 and the minimum score is 0.

The MMSE and ADAS-Cog are considered the gold standards for measuring cognitive function in AD. Due to the lack of an alternate gold standard for measuring changes in cognition, the validity of the MMSE for use in the clinical assessment of AD was reviewed against factors other than cognitive ability, such as

brain pathology, global assessments of AD as well as activities of daily living and quality of life assessments.

Overall changes in MMSE scores reflect physiological changes in the brain, suggesting it is a valid approach to scaling the severity of AD. The MMSE was also found to correlate with other global scales of AD (Clinical Dementia Rating and Global Deterioration Scale), although there is some variability in the results. Conversely, the MMSE appears to be of limited value in estimating quality of life and ability to conduct activities of daily living in people with AD.

The average rate of change (as measured by the MMSE) over a year for a person with AD is reported to be about 2 to 4 points – but it is unclear whether this change is due to measurement error or a reflection of the natural progression of cognitive impairment.

The MMSE measures changes in mental function over time but its reliability in assessing cognition varies, particularly when measured over shorter timeframes and in patients at differing stages of the disease. It appears to give a more reliable measure of changes in mental capacity when used over longer periods of time. The MMSE may have limited use in measuring cognitive change in individuals with AD who are followed for less than three years.

The MMSE has been found to be reliable between successive tests on the same individual, although test scores may be influenced by learning or coaching effects and the ratings given by different assessors.

The change in MMSE that is considered clinically significant or important ranges from a 3 to 5 point change in a patient's score. However this may depend on the severity of dementia as the MMSE is not a linear scale. That is, a change of 1 point in a person with mild dementia may not be the same as a change of 1 point in a person with moderate dementia. Variations can also occur because of the clinical setting in which assessment is carried out, patient demographics and the presence of other diseases.

Overall the findings of this review suggest that clinicians must be cautious when interpreting small changes in MMSE scores. Small changes have a reasonable chance of being caused by measurement error or the effect of a patient's experience in taking the assessment and improving their results when repeated over short intervals.

The MMSE is a simple and easy test to administer. The scoring broadly reflects severity of dementia in AD. This test was originally chosen by PBAC, in consultation with clinicians and stakeholders, to be the most practical and suitable assessment to objectively assess response to treatment with CEl. However, the test is less reliable for determining small changes in disease severity in some settings and when testing is repeated within short timeframes. Thus, the MMSE tool may not be as effective as anticipated in targeting treatment to only those who demonstrate improvement in disease symptoms due to treatment with a CEl or memantine.

Part 5 – Stakeholder consultation

This section of the report addresses input from stakeholders who contributed submissions addressing the review's terms of reference.

As well as the various components of the review, a full public consultation process was undertaken, in which any and all parties interested in providing input and evidence to this review were encouraged to do so. In addition, 63 stakeholders were invited directly to provide a submission.

Twenty-one submissions were received from a variety of stakeholders including families, carers, health professionals, non-government organisations and pharmaceutical companies. The general consensus was that these medicines should remain accessible to all Australians through the PBS.

The most commonly cited benefits associated with people taking these medicines included slower disease progression, improvements in behaviour and social skills, greater independence, more time spent lucid with families and less reliance on residential care.

Many considered assessment with the MMSE to be problematic and insensitive to mild cognitive changes. For example, it does not assess all the functional and behavioural improvements that can occur, such as improvements in activities of daily living and the quality of life of patients, the reduction of caregiver burden and nursing home avoidance. It also does not account for the effects of age, cultural background, social class, education status, poor vision or hearing, stroke and language.

Others considered that a stable MMSE score should be regarded as an improvement because it would be expected to decline every year. They also noted that small symptomatic benefits could make a big difference to patients and families, including improvements in the quality of life of carers and families, longer times spent at home and the delay of additional care and/or entry into residential care.

Some considered the MMSE to be useful because of the objectiveness of the measure and its usefulness in justifying stopping treatment to family members when a patient's symptoms continue to deteriorate.

Others considered observational-based assessment by carers and clinicians would be the best way to determine a patient's response to these medicines and subsequent changes in functional ability. Another submission considered that patients could be trialled without these medicines following admission to a high-level aged care facility.

Additionally, there were concerns raised about the use of anti-cholinergic medicines (particularly for incontinence) to treat the side effects of CElS and the risk of increasing use of anti-psychotic medicines should access to CElS and memantine be restricted further.

All published submissions can be accessed on the PBS website (pbs.gov.au) by following the links on the reviews tab under PBS news.

Part 6 – Review of the current PBS restriction and its effect on cost-effective use of these medicines

This section of the report addresses the fifth term of reference for the review.

TOR d) Review the current PBS restriction continuation rule and the likely effect it has on cost-effective utilisation of these medicines

PBAC can only recommend the Government subsidise medicines that represent 'value for money' or cost-effective use in the Australian healthcare setting. The PBS restriction for CElS and memantine was developed by PBAC and stakeholders to target treatment to people who showed meaningful improvement in cognitive and other symptoms of dementia after six months. The intention was to identify those who were most likely to benefit from these medicines and therefore limit use to

those in whom it was most likely to be cost effective as supported by the limited evidence.

While the review did receive comments from stakeholders that discussed the benefits of these medicines to patients and carers, the review did not identify any new or stronger evidence for cost effectiveness than that considered originally by PBAC. That is, the trial evidence identified in this review does not provide any further evidence that can be valued from a payer or government perspective to support or inform on the cost effectiveness of these medicines. However, there is significant evidence that these medicines are being used in a broader population than originally agreed as cost effective by PBAC. In addition, more recent trials have not demonstrated that more people will respond to these medicines according to the continuation criteria in the PBS restriction. In fact, the numbers of patients improving in the PBS population is likely to be lower, given those enrolled in trials are on average younger, are less likely to have other medical illnesses and are taking fewer medications that have the potential to interact with CElS.

Currently in Australia, more than twice as many people (60 per cent of those who initiate treatment) as those reporting cognitive improvement in clinical trials (28 per cent) continue taking PBS-subsidised CElS and memantine beyond six months. This pattern of use is not unusual and is similar to use in other countries, however other countries have different health funding systems. Thus, the number of people continuing treatment in Australia indicates the current PBS continuation rule is not effective in targeting use as originally intended. Prescribers are likely to be interpreting improvement in symptoms more subjectively or are applying the MMSE or ADAS-Cog scales with some degree of flexibility.

Given the available evidence on the effectiveness of these medicines and utilisation data that suggest at least 80 per cent of subsidised prescriptions for CElS and memantine are supplied for continuing use beyond six months, then it is likely that over half of these prescriptions are not cost effective as originally assessed by PBAC. The cost effectiveness of these medicines when used beyond 12 months, in full-time residential aged care and in those receiving cholinergic and sedative medicines also remains highly uncertain.