

Galantamine (Reminyl) prolonged-release capsules for dementia in Alzheimer's disease

Summary

- Prolonged-release galantamine has been PBS listed as an authority item for initial and continuing treatment of mild to moderate Alzheimer's disease. The listing was based on equivalence of the new formulation with the immediate-release formulation already listed on the PBS.
- There are no clinically relevant differences between prolonged-release and immediate-release galantamine.
- There is no reliable evidence of galantamine's long-term effectiveness. Short-term trials have found only modest improvements in scores on rating scales of cognitive, psychological and behavioural functioning.
- Galantamine has similar efficacy to other cholinesterase inhibitors.
- Increasing the dose of galantamine above 16 mg/day is not associated with greater benefit, and is likely to increase adverse effects.
- There is doubt about the place in therapy of cholinesterase inhibitors. Recent evidence with donepezil (Aricept) found no effect on long-term outcomes relevant to patients and carers such as delay in progression of disability or institutionalisation, behavioural and psychological symptoms and active carer time.

PBS Listing

The new PBS listing is for prolonged-release, once-daily formulations of galantamine (8 mg, 16 mg, 24 mg) for initial and continuing treatment of mild to moderately severe Alzheimer's disease. There is no change to the authority listing—see the *Schedule of Pharmaceutical Benefits* for the full authority requirements.

Reason for PBS listing

The PBAC considered the new once-daily capsules to be equivalent to the twice-daily tablets already listed on the PBS.¹

PBAC reviews found no benefit for higher doses of galantamine

An application for galantamine 12 mg immediate release tablets was rejected by PBAC in September 2003.² It was later recommended for listing in March 2004, but the PBAC stated that 'no evidence was presented that 12 mg twice daily provides any additional clinical benefits in terms of either effectiveness or toxicity over 8 mg twice daily'.³ Because there was no additional benefit, the PBAC recommended listing on the condition that should be no additional cost to the PBS for the prescribing of galantamine overall.

Place in therapy

- Guidelines suggest that patients who do not stabilise or improve in the first few months of anticholinesterase therapy are unlikely to have any subsequent benefit.⁴
- Patients should be reviewed regularly to assess the value of ongoing treatment.
- The clinical and cost-effectiveness of cholinesterase inhibitors is uncertain. While these drugs improve the quality of life of some people with Alzheimer's disease, clinical trials have found that, on average, improvements are modest.

The authority listing restricting the use of cholinesterase inhibitors to people with mild to moderate Alzheimer's disease improved by drug therapy reflects the evidence

- which is restricted to people with mild to moderate Alzheimer's disease
- that not all patients improve with cholinesterase inhibitors
- that it is not possible to predict which patients will respond to these drugs.⁴

Prolonged-release formulation no different to twice-daily tablet

The Reminyl Product Information states there are no clinically relevant differences between the prolonged-release once-daily formulation and the immediate release twice-daily tablets in terms of drug compliance, dose titration, dose reduction, discontinuation or dose compliance.⁵ It is of interest that there is no improvement in compliance in moving from a twice-daily preparation to a once-daily preparation.

Short-term effectiveness is modest

A Cochrane review⁶ of 3–6 month trials of galantamine found:

- cognitive function was improved marginally by galantamine compared to placebo (a change of between 2 to 4 points on the 70-point ADAS-Cog*)
- psychological and behavioural scores† were improved slightly in one six-month trial
- patients taking galantamine were between 1.3 and 3 times as likely as patients on placebo to be rated 'same' or 'improved' by physicians and carers (a subjective rating).

* ADAS-Cog: Alzheimer's disease assessment scale cognitive section

† Rated on the Neuropsychiatric Inventory

Additional benefit of long-term treatment is unclear

Three-year data exist only for a sub-group of patients who chose to stay on extended, open-label treatment after a randomised clinical trial—that is, those who probably responded well to treatment.⁷ Such results cannot be applied to previously untreated patients who might be eligible for treatment.

In a randomised year-long trial, most improvement in Mini-Mental State Examination (MMSE) scores occurred in the first 6 months of treatment, and declined gradually afterwards. After one year the score was similar to baseline.⁸

Galantamine has similar efficacy to other cholinesterase inhibitors

A meta-analysis reported similar effect sizes for donepezil, rivastigmine and galantamine.⁹ The maximum mean benefit achieved is similar across the class: for example, a 3-point improvement in the ADAS-Cog (a 70-point scale).¹⁰

Two trials comparing galantamine with donepezil do not show any consistent differences in efficacy.^{8,11} The longer of these, a 12 month comparison found no difference between the two drugs in the primary outcome of function in activities of daily living.⁸

Questions about effectiveness of cholinesterase inhibitors

The recent large AD2000 trial, which looked at long-term, real-life outcomes associated with **donepezil (Aricept)**¹², has raised doubts about the clinical relevance of statistically significant, but small, changes in rating scales seen in short-term studies. Although **galantamine was not studied** in the AD2000 trial, the questions raised apply to the whole class.

AD2000 found that donepezil improved scores on the MMSE and the Bristol Activities of Daily Living Scale (BADLS)* by about 1 point each over 2 years of treatment. Clinicians have indicated a change of 3 points as the minimally clinically relevant change in the MMSE for people with dementia.¹³ However in AD2000 there was

- no delay in progression of disability associated with Alzheimer's disease
- no delay in institutionalisation
- no change in behavioural and psychological symptoms
- no reduction in caregiver psychological morbidity (measured by the General Health Questionnaire—GHQ)
- minimal reduction in active carer time (reduced by 12 minutes per day, not statistically significant).¹²

It is possible the study was underpowered to detect differences in institutionalisation and progression of disability. Nonetheless changes on the MMSE and BADLS rating scales are consistent with those found in other trials.¹⁴

*BADLS: measures non-cognitive functioning and ability to perform tasks such as dressing, daily hygiene, mobility, communication.

Consider practical needs of patients and carers

After diagnosis, encourage patients and carers to make plans that take into account the patient's current functional state, as well as thinking broadly about what to do when deterioration occurs.

Changes to the person's environment, routines and tasks may help to reduce patient and carer distress in day-to-day activities. See the Alzheimer's Association website (www.alzheimers.org.au) for help sheets on daily care (hygiene, dressing, safety), behavioural issues (sundowning, wandering, aggression, agitation), and changes that can be made to the home and environment.

Consider the use of respite care. In Australia, the Commonwealth National Respite for Carers Program provides information and help to arrange access to respite care for carers of people with chronic conditions (www.health.gov.au/acc/carers/index.htm; phone 1800 059 059).

Some behavioural therapies (e.g. reorientation, reminiscence, music therapy) may be useful in some people with behavioural disturbance but clinical trials are small in size and few in number.¹⁵⁻¹⁷

GP-initiated Care Plans for people with chronic illness who require a multidisciplinary approach can be reimbursed through Medicare (www.health.gov.au/epc/careplan.htm#careplan).

Safety issues

Adverse effects such as nausea, vomiting, diarrhoea and dizziness appear to be similar to those of other drugs in the class¹⁸ and are increased at doses higher than 16 mg per day.⁶

Dosing issues

Starting dose: 8 mg per day for 4 weeks.

Galantamine 8 mg per day is used for titration to minimise adverse effects but is not a therapeutic dose.

Maintenance dose: 16 mg per day

Doses of galantamine above 16 mg per day are not associated with greater clinical improvement.^{6,9,19}

The maximum dose recommended in the product information is 24 mg per day. If 24 mg per day is prescribed, minimise adverse effects by ensuring at least 4 weeks at 16 mg per day before increasing the dose.⁵

Information for patients

Patients and/or carers should receive the Reminyl Consumer Medicine Information (CMI) from either their doctor or pharmacist.

The Alzheimer's Association of Australia offers support and information to people with Alzheimer's disease and their carers and families.

website: www.alzheimers.org.au

Phone (toll-free): 1800 639 331

References

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Date prepared: October 2004

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.