

# Memantine (Ebixa) for moderately severe Alzheimer's disease

(me-MAN-teen)

## Summary

- Memantine is PBS listed for use in moderately severe Alzheimer's disease. In contrast, the cholinesterase inhibitors are PBS listed for patients with mild to moderate Alzheimer's disease.
- Memantine does not stop the progression of Alzheimer's disease.
- Short-term trials have found modest improvements in scores on rating scales of cognitive, psychological and behavioural functioning. The clinical importance of these outcomes is yet to be established.
- There is no reliable evidence of memantine's long-term effectiveness.
- As with the cholinesterase inhibitors, not all patients respond to treatment. Review patients regularly and discontinue after 6 months if there is no improvement.
- There have been no head-to-head trials of memantine against any of the cholinesterase inhibitors.
- There is a lack of evidence on the efficacy of memantine among people who cannot tolerate or do not respond to a cholinesterase inhibitor. If switching, consider gradually reducing the dose of the cholinesterase inhibitor while gradually increasing the dose of memantine.
- Memantine is contraindicated in patients with renal impairment (creatinine clearance  $\leq 50$  mL/min) or a history of seizures.

## PBS listing

### Authority required

Initial and continuing treatment of moderately severe Alzheimer's disease as monotherapy. This is narrower than the TGA-approved indication for memantine to treat moderately severe to severe Alzheimer's disease.

The diagnosis of moderately severe Alzheimer's disease must be confirmed by a specialist, and the patient's baseline Mini-Mental State Examination (MMSE)\* score must be 10–14, inclusive. Memantine can be prescribed to patients with an MMSE score of  $\leq 9$  if the patient:

- is from a different cultural background
- has an intellectual or sensory disability
- has inadequate English, prominent dysphasia or very limited education.

In these situations the MMSE assessment must be supplemented with results of the Clinician's Interview Based Impression of Severity (CIBIS).

Continuing treatment requires a demonstrated improvement in cognitive function within 6 months of initiating therapy, as measured by a 2-point increase in the baseline MMSE score, or, in those for whom the CIBIS was used to assess disease severity, by a rating of 'very much improved' or 'much improved' on the Clinician's Interview Based Impression of Change (CIBIC)<sup>†</sup> scale.

The PBS only allows treatment with one PBS-subsidised drug (memantine or a cholinesterase inhibitor) at a time.

\* A 30-point cognition scale in which lower scores indicate poorer function. The Standardised Mini-Mental State Examination (SMMSE) may also be used to assess baseline cognition.

† A 7-point subjective overview of a patient's improvement in general and across the domains of cognition, functional ability and behaviour.

## Reason for PBS listing

Several previous applications for memantine to be PBS listed for Alzheimer's disease were rejected by the Pharmaceutical Benefits Advisory Committee (PBAC).<sup>1</sup> While the successful submission argued that memantine was no worse than the cholinesterase inhibitors (donepezil, rivastigmine and galantamine), the PBAC disagreed.<sup>2</sup> Instead, memantine was recommended for listing on 1 July 2008 after the PBAC decided that, while the drug was less effective than the cholinesterase inhibitors (although this was associated with some uncertainty), it was also less costly and was associated with fewer adverse effects.

## Place in therapy

Memantine is an *N*-methyl-D-aspartate (NMDA) antagonist that is thought to protect against elevated levels of glutamate. Memantine is PBS listed for the treatment of moderately severe Alzheimer's disease (MMSE 10–14). In contrast, the cholinesterase inhibitors — which are an unrelated pharmacological class — are PBS listed for the treatment of mild to moderate Alzheimer's disease (MMSE 10–24).

Like the cholinesterase inhibitors, memantine does not stop the progression of Alzheimer's disease. Clinical trials of memantine have shown benefits over a 6-month period.

Not all patients respond to treatment with drugs for the symptomatic treatment of dementia. Guidelines suggest that patients who do not stabilise or improve in the first few months of therapy are unlikely to have any subsequent benefit.<sup>3</sup> Patients should be reviewed regularly and the drug discontinued if they do not improve — i.e. if they do not achieve a MMSE score 2 points above their baseline score.

### Short-term effectiveness is modest

No studies have been performed solely among people with **moderately severe** Alzheimer's disease (MMSE score 10–14). However, some information on the efficacy of memantine can be inferred from trials among people with **moderate to severe** Alzheimer's disease (MMSE 3–14) and trials among people with **mild to moderate** Alzheimer's disease (MMSE 10–23).

A Cochrane review<sup>4</sup> of 6-month trials of memantine in people with **moderate to severe** Alzheimer's disease

reported marginally less deterioration among people taking memantine compared with those taking placebo. These included:

- a difference of 3.0 points on a 100-point measure of cognitive function
- a difference of 1.3 points on a 54-point scale of functional ability
- a difference of 2.8 points on a 144-point measure of behaviour and mood
- a 0.3 point difference on a 7-point subjective clinical impression of change scale.

While these differences are statistically significant, they are small and may not represent a clinically meaningful change. Long-term trials of memantine are required to assess whether these differences translate into improvements in patient outcomes (e.g. delaying institutionalisation).

Memantine did not show the same effects among people with less severe Alzheimer's disease. Analyses performed in the Cochrane review of 6-month trials of memantine in patients with **mild to moderate** Alzheimer's disease found that memantine had no benefit on behaviour or functional ability compared with placebo and made only a 1-point difference on a 70-point cognitive assessment tool (the ADAS-cog).<sup>4</sup> A 4-point difference is commonly accepted as being clinically detectable on this scale.<sup>3</sup>

### Only some patients will respond to drug therapy

Review patients regularly and continue drug therapy only if cognition improves within 6 months of initiating therapy ( $\geq 2$  points increase from baseline MMSE score).

While an improvement on an assessment scale may be statistically significant, this may not translate into a clinically meaningful benefit. In trials in which patients were classified according to whether they showed a predefined clinically meaningful response only some responded to memantine therapy.

Bakchine et al defined responders as patients showing marked improvement in cognitive function (change in ADAS-cog score  $\geq 4$ ) and global stabilisation or improvement (CIBIC+ score  $\geq 4$ ). At 6 months there was no significant difference in the proportion of patients receiving placebo (25%) and those receiving memantine (31%) who met this definition.<sup>5</sup>

Reisberg et al defined responders as patients with stabilisation or improvement on CIBIC+ and an improvement or no change in cognition **or** disability. At 28 weeks, 29% of patients on memantine and 10% of patients on placebo were classified as responders ( $p < 0.001$ ).<sup>6</sup>

### The benefit of long-term treatment is unproven

No randomised trial of memantine in Alzheimer's disease has studied efficacy for more than 7 months. Efficacy data exist for a subgroup of patients who chose to stay on extended open-label memantine *after* participating in a randomised clinical trial.<sup>‡</sup> This may introduce bias because people who continued open-label memantine were most likely those who responded to treatment and tolerated the drug.

During a 6-month extension study the condition of patients who had received memantine in the initial randomised trial continued to deteriorate. Functional ability deteriorated significantly faster during the second 6-month period while cognition continued to decline at a steady rate.<sup>7</sup>

### There are no head-to-head trials of memantine and the cholinesterase inhibitors

There are no head-to-head comparisons of memantine with any of the cholinesterase inhibitors. An indirect comparison was made in the PBAC submission, comparing randomised trials of memantine against randomised trials of the cholinesterase inhibitors, using placebo as the common comparator. Ideally a head-to-head randomised trial comparing memantine with the cholinesterase inhibitors would help define relative efficacy.

### There is limited evidence to support combination therapy with memantine and a cholinesterase inhibitor

There is limited evidence to support combination therapy. A 6-month randomised trial ( $n = 404$ ) in patients with moderate to severe Alzheimer's disease reported that those taking memantine and donepezil performed marginally better on measures of cognition, function and behaviour than people taking donepezil and placebo.<sup>9</sup>

In contrast, a 6-month randomised trial ( $n = 433$ ) of addition of memantine or placebo to a stable dose of a cholinesterase inhibitor (donepezil, rivastigmine or galantamine) in patients with mild to moderate Alzheimer's disease found no difference between the groups.<sup>10</sup>

The PBS listing only allows subsidisation of either memantine or a cholinesterase inhibitor.

### A lack of evidence on the efficacy of switching from a cholinesterase inhibitor to memantine

There is a lack of evidence on the efficacy of memantine among people who are unable to tolerate or do not respond to a cholinesterase inhibitor. Hypothetically, memantine could benefit these patients, as it has a different mechanism of action to that of the cholinesterase inhibitors.

A single 8-week switching study among patients who no longer benefited from donepezil has been published.<sup>11</sup> Participants began memantine after either stopping donepezil abruptly ( $n = 24$ ) or gradually tapering their donepezil dose over 2 weeks ( $n = 22$ ). During the first week, 4 patients in the abrupt discontinuation group experienced an adverse event (arthrosis, pruritus or vertigo) while none were reported in the tapered group. The study was not designed to assess efficacy.

Memantine is only PBS approved for patients with an MMSE score of 10–14. If switching a patient who meets this criterion, consider gradually reducing the cholinesterase inhibitor dose. The memantine dose may be gradually increased while tapering the dose of cholinesterase inhibitor or after it has been stopped.

### Fewer people taking memantine developed agitation compared with placebo

During clinical trials against placebo, agitation was significantly less commonly reported among patients with moderate to severe Alzheimer's disease who took memantine, compared with those using placebo. The effect is small, as 17 patients needed to be treated for 6 months to prevent 1 case of agitation.<sup>4</sup>

<sup>‡</sup> A second open-label extension trial only investigated safety and tolerability and did not report any efficacy data.<sup>8</sup>

## Safety issues

Memantine is contraindicated in patients with renal impairment (creatinine clearance  $\leq$  50 mL/min) or a history of seizures.<sup>12,13</sup>

In clinical trials up to 25% of participants stopped taking memantine; in 6% to 12% of participants this was because of adverse effects.<sup>5,6,9,10,14,15</sup> However, adverse effects are more difficult to assess in patients with later-stage dementia<sup>16</sup> so these rates may be an underestimate.

Common adverse effects include confusion, dizziness, drowsiness, headache, insomnia, agitation and hallucinations.<sup>12</sup> In one clinical trial hypertension was more common in the memantine group than in the placebo group (7.9% vs 2.3%,  $p = 0.01$ ).<sup>15</sup> There have been single case reports of hepatitis with cholestasis<sup>17</sup>, psychosis<sup>18</sup>, spontaneous bruising<sup>19</sup> and exacerbation of myoclonic jerks.<sup>20</sup>

Avoid using other *N*-methyl-D-aspartate antagonists (amantadine, ketamine, or dextromethorphan) with memantine, as this may increase both the incidence and severity of adverse effects.<sup>13</sup>

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website ([www.tga.gov.au](http://www.tga.gov.au)).

## Dosing issues

Memantine is available as a 10 mg tablet or 10 mg/mL oral solution with a calibrated dropper. The recommended maintenance dose is 20 mg/day (10 mg twice a day). Start memantine as shown in Table 1.

Take memantine (tablets and drops) with liquid. Memantine can be taken with or without food.

**Table 1: Initial dose titration**

Week	Dose
Week 1	<b>Morning:</b> half a tablet or 10 drops of solution
Week 2	<b>Morning:</b> half a tablet or 10 drops of solution <b>Evening:</b> half a tablet or 10 drops of solution
Week 3	<b>Morning:</b> 1 tablet or 20 drops of solution <b>Evening:</b> half a tablet or 10 drops of solution
Week 4	<b>Morning:</b> 1 tablet or 20 drops of solution <b>Evening:</b> 1 tablet or 20 drops of solution

## Information for patients and carers

Discuss the following with the patient and/or carers:

- memantine does not work for everyone and the response to the drug cannot be predicted
- common adverse effects include confusion, dizziness, drowsiness, headache, insomnia, agitation and hallucinations
- drug therapy will be trialled for 6 months
- continuing the drug after 6 months requires demonstrated improvement in cognitive function as measured by an increase of at least 2 points from baseline on the MMSE.

Discuss the Ebixa consumer medicine information (CMI) leaflet.

Alzheimer's Australia (toll free 1800 100 500) offers information and support for people with Alzheimer's disease and their carers and families.

The Commonwealth National Respite for Carers Program provides information and help to arrange access to respite care for carers of people with chronic conditions (phone 1800 059 059).

## References

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Date prepared: June 2008

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.