

# NEW DRUG EVALUATION

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## MEMANTINE

Memantine is an NMDA antagonist for the treatment of moderately severe to severe Alzheimer's disease (AD). Published evidence suggests that memantine may slow the decline in functional and global outcomes in some patients, rather than improve them. Memantine appears to be well tolerated. Acetylcholinesterase inhibitors (AChEI) remain the pharmacological treatment of choice for patients with AD. However, memantine may be considered on an individual basis with careful monitoring of side effects and benefits, for patients who are unsuitable or have not been considered for treatment with an AChEI.

### *What is it?*

Memantine (Ebixa®, Lundbeck) is an N-methyl-D-aspartate (NMDA) antagonist licensed for the treatment of patients with moderately severe to severe Alzheimer's disease (AD). It blocks NMDA receptors, reducing glutamate-mediated neurotransmission. Excessive glutamate activity is neurotoxic and may contribute to the progression of AD.<sup>1</sup> This mechanism of action contrasts with that of the cholinesterase inhibitors (donepezil, rivastigmine and galantamine), which augment cholinergic function. The initial dose is 5 mg daily; this is increased by weekly increments of 5 mg/day to the recommended maintenance dose of 20 mg daily. Memantine is available as 10 mg tablets and as a 10 mg/ml oral solution.

### *How effective is it?*

A randomised double-blind placebo-controlled trial was conducted in patients with moderately severe to severe AD.<sup>1</sup> 252 patients were randomised and 181 completed the study. Memantine 10 mg twice daily was given over 28 weeks. The primary end-points included a global assessment (using the Clinicians Interview-Based Impression of Change, CIBIC) and a functional assessment (using the activities of Activities of Daily Living Inventory, ADCS-ADL). The results of these favoured memantine over placebo  $p=0.025$  and  $p=0.003$  respectively.<sup>1</sup> After completing the double blind period of the study all patients were given the opportunity to enter the 24-week open-label period. Patients who had switched from placebo to memantine showed some improvement in their deterioration rate (in both primary variables).<sup>2</sup>

A multi-centre, double-blind trial in 166 patients with severe dementia (49% AD and 51% vascular dementia)

used the lower dose of 10 mg memantine daily for 12 weeks.<sup>3</sup> In the 79 patients with AD, memantine treatment was significantly better than placebo for both primary endpoints (functional and global). There was insufficient evidence to propose memantine for the treatment of vascular dementia.<sup>3</sup>

A Cochrane review on memantine has recently been published. It concluded that memantine has a possible benefit on cognition and global measures, and an early improvement in behaviour in people with dementia.<sup>4</sup>

### *How safe is it?*

Memantine has been on the market in Germany for about 20 years without apparent cause for concern.<sup>5</sup> In clinical trials adverse reactions that were more common with memantine than placebo included hallucinations (2% vs. 0.7%), confusion (1.3% vs. 0.3%), dizziness (1.7% vs. 1%), headache (1.7% vs. 1.4%) and tiredness (1% vs. 0.3%).<sup>6</sup>

Drugs with similar activity (ketamine, dextromethorphan and amantadine) may increase the risk of adverse effects and should be avoided.

The dose should be halved in patients with moderate renal impairment. There is no data on the use of memantine in patients with severe renal impairment or impaired hepatic function. In theory other drugs using the same renal transport system as memantine may also interact leading to a potential risk of increased plasma levels (e.g., cimetidine, ranitidine, quinine and nicotine).<sup>6</sup>

### *What other options are there?*

The National Institute for Clinical Excellence (NICE) has published guidance on the use of cholinesterase inhibitors (AChEIs) for the treatment of mild to

moderate AD.<sup>7</sup> It is due to be reviewed in December 2003. Memantine is currently the only licensed treatment available for patients with moderately severe to severe AD.

### When should it be used?

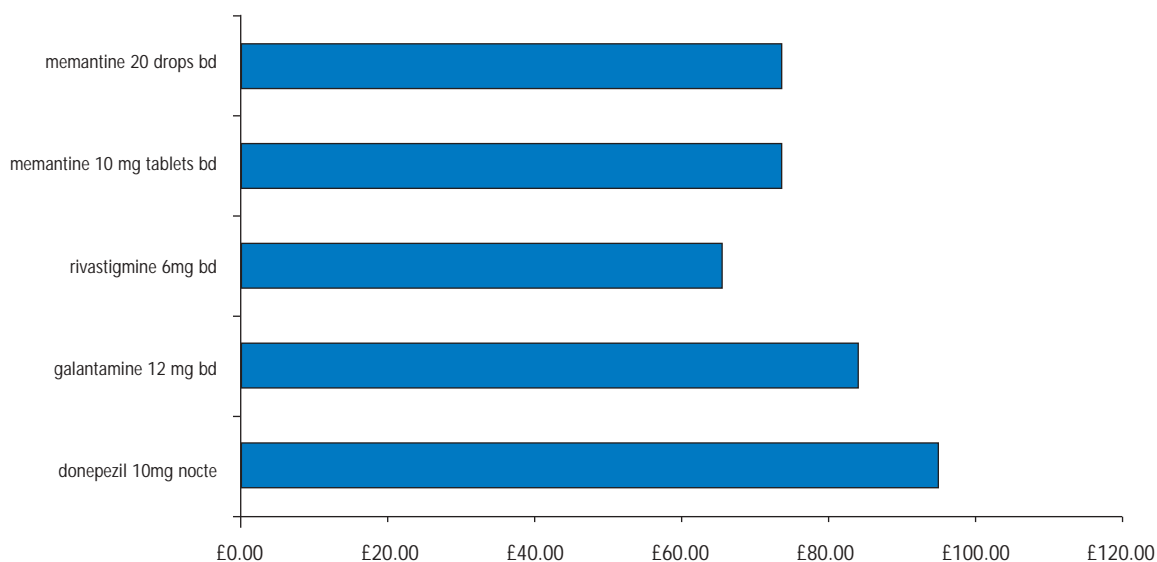
The place of memantine in the management of AD is currently uncertain. If memantine is to be used, treatment should only be initiated and supervised by a physician experienced in the diagnosis and treatment of AD. The Royal College of Psychiatrists have recently published interim guidance for the use of memantine

for AD. It states that 'AChEIs remain the pharmacological treatment of choice for patients with AD. However, memantine may be considered on an individual basis for selected patients in whom an AChEI, for whatever reason, is unsuitable'.<sup>8</sup> There is no published evidence supporting the superiority or safety of co-administration of memantine with any of the AChEIs over monotherapy.<sup>8</sup>

The manufacturer recommends that treatment should be continued for 3-6 months before discontinuation is considered.<sup>9</sup>

### How much does it cost?

Cost for 28 days treatment (prices from MIMS March 2003)



NB. Rivastigmine, galantamine and donepezil are licensed for the treatment of mild to moderately severe AD only. Doses shown are for general comparison only and do not imply therapeutic equivalence.

### REFERENCES

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A- abstract, E-editorial

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