

## NEW MEDICINES ON THE MARKET

### Evaluated information for the NHS

## Memantine

### Summary

- Memantine (Ebixa®) is the first drug to be licensed for moderately severe to severe Alzheimer's disease (AD). It is a N-methyl-D-aspartate (NMDA) antagonist. Its mechanism of action differs from the other licensed treatments for AD, the acetylcholinesterase inhibitors, which are licensed for mild to moderate disease.
- The efficacy of memantine in the treatment of moderately severe to severe AD has been evaluated in two multicentre randomised controlled trials (RCTs). In the pivotal trial (n=252, dropout rate 28%) patients' symptoms and condition deteriorated in both the memantine and placebo study groups during the 28 week study. However, the deterioration was reported to be smaller in the memantine group (difference in clinical global status p=0.06 [95%CI: -0.05, 0.02], functional capacities p=0.02 [95%CI: 0.49,3.78]). A 6 month open label extension to this study is yet to be published.
- Results of the second trial, which included 166 patients with AD or vascular dementia, showed statistically significant improvements in functional and global endpoints with memantine at 12 weeks. An RCT investigating memantine in combination with acetylcholinesterase therapy in moderate to severe AD had promising results but cannot be properly assessed until fully published.
- In clinical trials, memantine was generally well tolerated. The most frequent adverse events reported were dizziness, headache and fatigue. Agitation occurred less frequently with memantine than placebo. Memantine has been licensed in Germany for over 10 years for the treatment of dementia syndrome without apparent safety concerns.
- The place in therapy of memantine is yet to be determined. Clinical trials have shown some statistically significant benefits in functional and global outcomes, however the key trial showed a slowing in deterioration rate rather than an improvement in the condition. The clinical significance of the small differences found in the studies is open to debate. The Scottish Medicines Consortium recently advised that associated gains appear to be marginal relative to the overall costs of memantine. A NICE appraisal of memantine is expected in 2005.

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## MEMANTINE

<b>Approved Name:</b>	Memantine
<b>Brand Name: (Manufacturer):</b>	Ebixa (Lundbeck)
<b>Presentation:</b>	10mg tablets and 10mg/g oral drops
<b>BNF Therapeutic Class:</b>	N-methyl-D-aspartate (NMDA) receptor antagonist BNF 4.11 Drugs for Dementia
<b>Licensed Indications:</b>	Treatment of moderately severe to severe Alzheimer's disease.
<b>Dosage and Administration:</b>	Treatment should be started with 5mg daily for the first week, followed by 10mg per day for the second week and 15mg per day for the third week. The recommended maintenance dose, from the fourth week, is 20mg per day. Maximum daily dose is 20mg.
<b>Sector of Use:</b>	Hospital [Y] Primary Care [Y ]  Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Therapy should only be started if a caregiver is available who will regularly monitor drug intake by the patient.

<b>Therapeutic Comment:</b>	Memantine is the only drug licensed for the treatment of moderately severe to severe AD. Its mechanism of action differs from the other drugs licensed for AD, the acetylcholinesterase inhibitors. Clinical trials have shown some statistically significant benefit in functional and global outcomes. It is unclear whether these benefits are clinically important and more studies are needed to determine its place in therapy.
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<b>Cost and Course Details:</b>	<b>28 days treatment</b> (MIMS August 2003) 20mg per day - £74.20
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<b>Treatment Alternatives:</b>	<b>28 days treatment</b> (MIMS August 2003) acetylcholinesterase inhibitors:- Donepezil 10mg on £95.76 Rivastigmine 6mg bd £68.04 Galantamine 12mg bd £84.00  The acetylcholinesterase inhibitors are licensed for the treatment of mild to moderately severe AD only.
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## INTRODUCTION

Memantine was launched in the UK in September 2002 for the treatment of moderately severe to severe Alzheimer's disease (AD). It is a non-competitive and low affinity NMDA receptor antagonist. It is the first NMDA antagonist licensed for use in AD and the first drug licensed for advanced AD. Its suggested mechanism of action differs from the other drugs licensed for AD, which are acetylcholinesterase inhibitors and are licensed for mild to moderate AD. Memantine has been licensed in Germany for the treatment of dementia syndrome for over 10 years.

Dementia is a chronic progressive mental disorder that adversely affects memory, thinking, comprehension, judgement, orientation, calculation and language. AD is the most common form of dementia [1]. Estimates of numbers of people with AD differ, because of the difficulties in diagnosis and different classifications of stages of the disease. However it has been estimated that approximately 700,000 people in England and Wales have dementia. Of these about 400,000 have AD. Other forms of dementia include vascular dementia (VaD) and mixed dementia [1].

In January 2001 NICE issued guidance on the use of the acetylcholinesterase inhibitors donepezil, rivastigmine and galantamine for the treatment of AD. These three drugs are licensed in the UK for the treatment of mild to moderate disease. The NICE guidance recommends that one of these drugs should be available for patients under the care of a specialist clinic and whose Mini Mental State Examination (MMSE) score is above 12 points and who fulfil certain criteria.

Memantine is currently the only drug licensed for use in moderately severe to severe AD. A NICE appraisal on memantine is expected in May 2005.

## PHARMACOLOGY

Memantine is a non-competitive, moderate-affinity NMDA receptor antagonist [2]. There is increasing

evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia. [2] Glutamate is the principal fast neurotransmitter in the brain. The NMDA receptor is a glutamate-gated ion channel, which permits passage of calcium ions into the neuron [3]. An excessive influx of calcium ions may be toxic to the neuron. By blocking the NMDA receptor, memantine blocks the effects of pathologically elevated levels of glutamate that may lead to neuronal dysfunction [2]. This mechanism of action differs from the acetylcholinesterase inhibitors which augment cholinergic function.

## PHARMACOKINETICS

(see SPC)

Memantine is rapidly and completely absorbed following oral administration and peak serum levels are observed within 6-8 hours. It demonstrates linear pharmacokinetics. The volume of distribution is around 10L/kg. About 45% of memantine is bound to plasma proteins. Memantine appears to concentrate in the brain and cerebrospinal fluid. It is primarily eliminated as the parent drug via the kidneys (75% to 90%) and its terminal half-life is 60-100 hours [2,4].

Memantine is only metabolised to a minor extent and into inactive metabolites, therefore clinically relevant changes in pharmacokinetics are not expected in mild to moderate liver impairment [2].

## EFFICACY

The outcome measures used for assessing patients with dementia in clinical trials consist of a number of structured test systems. The test systems evaluate the patient in a variety of domains:- cognitive, global, behavioural and functional; and are described in the table overleaf.

**Table 1: Test Systems Used in the Trials**

Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-cog)	Comprises 11 individual tests, spoken language ability, comprehension of spoken language, recall of test instructions, word finding difficulty, following commands, naming object, construction drawing, ideational praxis, orientation, word recall and word recognition. The total score ranging from 0-70, the high score indicating greater impairment [5].
Alzheimer’s Disease Cooperative Study – Activities of Daily Living (ADCS-ADL)	Specifically designed for Alzheimer’s disease. A structured questionnaire designed to determine a patients ability to perform one of the activities of daily living ranging from total independence to total inability. The ADCS-ADLsev is modified for more severe dementia with a total score of 54 signifying optimal performance [5,6].
Behaviour Rating Scale for Geriatric Patients (BGP)	An observer-rated scale for the assessment of functional and behavioural disturbances of geriatric patients, performed by nursing staff. The BGP contains four sub scales and the largest one “care dependence” measures the activities of daily living [5].
Clinical Global Impression of Change (CGIC)	A global assessment of all domains of a patient's current condition in comparison with baseline. It is a 7 point scale, from 1 (very much improved) to 7 (very much worse). The rating is conducted by the same clinician, at both time points with input from carers [5].
Clinicians Interview-Based Impression of Change (CIBIC-plus)	A global rating of function in four areas, general, cognitive, behaviour and activities of daily living. All patients are scored as 4 at baseline and subsequent assessments on a scale of 1-7 are relative to baseline, with 1 showing marked improvement and 7 marked worsening. Information is obtained from the caregiver and the patient [5].
Mini Mental State Examination (MMSE)	A simple method of grading cognitive status. It consists of 11 tests heavily dependent on language-based items. Score range 30 (normal) to < 6 (severe dementia).
Severe Impairment Battery (SIB)	This was designed to evaluate cognitive performance in advanced Alzheimer’s disease. It is a 51 item scale which includes an assessment of social interaction, memory, language and construction. The scores range from 0 (greatest impairment) to 100 [7].

**Moderately severe to severe AD**

Evidence relating to the efficacy of memantine in its licensed indication is largely derived from a recently published pivotal phase III randomised double blind trial [6]. The 28 week trial conducted at 32 US centres compared oral memantine (20mg per day) to placebo in outpatients with moderately severe to severe AD. All patients had to be living in the community with reliable caregivers. Exclusion criteria included vascular dementia, dementia or neurological disease due to conditions other than AD and major depression. 252 patients (67% women; mean age, 76 years) were enrolled. Primary endpoints were a global and functional assessment. The global domain was

assessed using the Clinicians Interview-based Impression of Change Plus Caregiver Input (CIBIC-Plus) and function was measured using the Activities of Daily Living modified for more severe dementia (ADCS-ADLsev). Secondary efficacy endpoints included a measure of cognition using Severe Impairment Battery (SIB). Efficacy variables were assessed at baseline, 12 weeks and 28 weeks or at early termination, with a 28 week retrieved-dropout visit when possible (only 5 of the 71 dropouts returned for evaluation at week 28). The main analysis was conducted in patients who received at least one assessment after baseline. For those who discontinued treatment early the most recent previous observation was carried forward and used as

the final result (intention to treat (ITT) population) with the last observation carried forward (LOCF)). The results were also analysed with only the observed values included, without replacing the missing values, based on randomised patients who were available for evaluation at week 28 (observed-cases analysis).

Of the 252 patients enrolled, 181 (72%) patients completed the study and were evaluated at week 28. Dropout rate was relatively high as 71 patients (28%) discontinued treatment early:- the authors attribute this to the severity of the disease stage in the study group. The withdrawal rate was higher in the placebo group (42 (33%) patients) than the memantine group (29 (23%) patients). Dropouts were due to adverse events in 22 (17%) patients in the placebo group and 13 (10%) patients in the memantine group. Other reasons for dropout (placebo vs. memantine) included refusal of ongoing participation (11% vs 10%), death (3% vs 1%), protocol violation (2% vs 2%) and change of caregiver (2% vs 0). Failure to obtain information at week 28 for the majority of dropouts limits the interpretation of the results (average duration of randomly assigned therapy was 24 weeks for both study groups).

The patients' symptoms and condition deteriorated in both study groups during the 28 weeks. However the deterioration was smaller in the memantine group. The CIBIC-Plus results showed a mean difference in favour of memantine of 0.3 points ( $p=0.06$  non significant; 95%CI -0.05 to 0.02) in the LOCF population ( $n=236$ ) and 0.3 points ( $p=0.03$ ; 95%CI -0.69 to -0.03) in the observed cases ( $n=181$ ) at week 28. Although statistically significant in the observed cases, the clinical significance of a 0.3 point difference on a 7 point scale is not clear.

The ADCS-ADLsev results showed significantly less deterioration in the memantine group than in the placebo group. In the LOCF analysis ( $n=247$ ) the mean difference was 2.1 ( $p=0.02$ ; 95%CI 0.49 to 3.78). In the observed cases analysis ( $n=181$ ) the mean difference was 3.4 ( $p=0.003$ ; 95%CI 1.45 to 5.28). Again it is not

clear how significant a 3.4 point difference is clinically on a 54 point scale.

The SIB scores also favoured the memantine group (mean difference 6.1,  $p<0.001$  in the LOCF analysis  $n=247$ ; mean difference 5.7,  $p=0.002$  for observed cases; confidence intervals not stated).

The authors acknowledge that point differences between drug and placebo treated patients on quantitative scales do not necessarily indicate clinically meaningful effects. In order to illustrate clinical relevance of results response analysis (rates of individual response) is often performed. This study reported a significant difference in the predefined criterion for a response, incorporating multiple end points, with 29% of patients receiving memantine and 10% of those receiving placebo having a response  $p<0.001$ . Although not a primary outcome measure, the authors presented a LOCF analysis of caregiver time. The analysis suggested that patients receiving memantine appeared to need 45.8 hours less caregiver time each month than those receiving placebo. Memantine appeared to be well tolerated, with a similar frequency of adverse effects occurring in each study group except for agitation which was more frequent in the placebo group (32% vs 18%) and may indicate a beneficial effect.

On completion of the 28 week double blind study patients were invited to enter a 24 week open-label extension [8]. 175 patients (69%) entered the extension period. The results are yet to be fully published. Patients who were switched from placebo to memantine showed some improvement in their rate of deterioration (relative to their projected rate of decline) in both primary end points, CIBIC-plus and ADCS-ADLsev ( $p$  values not stated).

A second RCT [9], the 9M BEST study, was a 12 week randomised, double blind trial conducted at 7 centres in Latvia ( $n=166$ ). It compared oral memantine, at the lower dose of 10mg per day to placebo, in care-dependant in-patients with moderately severe to severe

dementia of mixed type (49% AD, 51% VaD). Functional and global domains were measured as primary endpoints. The global domain was assessed using Clinical Global Impression of Change (CGI-C) rated by physician and function was measured using Behavioural Rating Scale for Geriatric Patients subscore 'care dependence' (BGP) rated by nursing staff. The ITT sample comprised 166 patients and 151 patients were treated per protocol (PP). At 12 week ITT endpoint analysis, a positive response in general symptoms (CGI-C) was seen in 73% versus 45% in favour of memantine ( $p < 0.001$ ). The difference in the BGP subscore care dependence was also statistically significant in favour of memantine ( $p = 0.016$ ). *Post hoc* analysis indicated similar benefits in AD and VaD subgroups.

The Royal College of Psychiatrists have issued interim guidance on the use of memantine for AD. It states that acetylcholinesterase inhibitors remain the pharmacological treatment of choice for patients with AD. However memantine could be considered on an individual basis, with careful monitoring of side effects and benefits, in carefully selected patients in whom an acetylcholinesterase inhibitor, for whatever reason, is unsuitable [10].

The Scottish Medicines Consortium (SMC) recently advised that the magnitude of benefit is extremely small for memantine in moderately severe to severe AD [11]. They stated that compared with placebo, memantine is associated with a statistically significant reduction in the rate of deterioration in global, functional and cognitive scales. The SMC recommended that memantine should not be used within NHS Scotland because, on the evidence presented, the associated gains appear to be marginal relative to the overall costs [8]. Lundbeck has indicated to the SMC their decision to resubmit.

### Combination Therapy

The results of the first RCT investigating memantine and donepezil combination treatment of moderate to severe AD have been presented at a conference but

not yet fully published [12]. 403 patients (mean age 76 years) were treated with either memantine (20mg/day) or placebo in addition to donepezil (stable dose of 5 or 10mg/day) and assessed after 24 weeks. Mean MMSE score at entry was 10. Primary efficacy variables were a measure of cognition (SIB) and function (ADCS-ADL). 395 patients entered ITT analysis. At week 24 the combination group showed statistically significantly less decline in daily function (ADCS-ADL  $p = 0.028$ ). The authors state that treatment with combination therapy resulted in improved cognitive performance relative to baseline, whereas treatment with donepezil alone was associated with continued cognitive decline. These results look promising but cannot be properly assessed until the study is fully published.

### Vascular Dementia

The efficacy of memantine in the treatment of mild to moderate VaD has been evaluated in two RCTs [13,14]. Memantine is currently not licensed for this indication.

MMM 300 was a multicentre, 28 week, randomised double blind trial carried out in France in 321 patients (mean age 76 years) [13]. It compared memantine 20mg per day to placebo in patients with probable VaD and a MMSE score between 12 and 20. The two primary endpoints were a cognitive assessment (ADAS-cog) and a global rating (CIBIC-Plus). 288 patients were available for ITT analysis. At 28 weeks the mean ADAS-cog scores were significantly improved relative to placebo. In the ITT population, the memantine group mean score gained an average of 0.4 points whereas the placebo group mean score had fallen by 1.6 points i.e. a difference of 2 points (95%CI: 0.49 to 3.60). The difference in ITT response rates for CIBIC-Plus was not statistically significant (60% with memantine compared with 52% with placebo).

The second larger RCT, MMM 500, had a similar design and was carried out in 57 UK centres [14]. 579 patients with probable VaD and MMSE scores between

10 and 22 were randomised and 548 patients with at least one post baseline efficacy assessment entered ITT analysis. The authors state that at 28 weeks memantine was shown to improve cognition relative to placebo. The ADAS-cog scores differed by a mean of -1.75 points (95%CI: -3.023 to -0.49) and a median of 2 points between the two groups. However differences in CGI-C ratings were not significant.

It is unclear whether the ADAS-cog rating, used in both these studies, is a suitable assessment tool for dementia other than Alzheimer's disease.

### ADVERSE EFFECTS

(see SPC)

Memantine was well tolerated in trials. The main adverse reactions involve the central nervous system and are dose dependent [4]. Common adverse reactions (occurring in 1-10% of patients) are hallucinations (2.0% memantine vs. 0.7% placebo), confusion (1.3% vs. 0.3%), dizziness (1.7% vs. 1.0%), headache (1.7% vs. 1.4%) and tiredness (1.0% vs. 0.3%). Post marketing safety experience from the German market, where more than 100 million daily doses of memantine have been sold, has not given apparent cause for concern.

### CONTRAINDICATIONS AND PRECAUTIONS

Memantine is not recommended in patients with severe renal impairment ( $\text{CrCl} < 9 \text{ml/min/1.73m}^2$ ) due to lack of data. In patients with moderate renal impairment ( $\text{CrCl} 40\text{-}60 \text{ml/min/1.73m}^2$ ) the daily memantine dose should be reduced to 10mg per day [2].

Alkalinisation of urine may reduce renal elimination of memantine leading to a possible increase in side effects necessitating careful monitoring. Alkalinisation of urine may result from drastic changes in diet e.g. from a carnivore to a vegetarian diet or a massive ingestion of alkalisating gastric buffers. Urine pH may

also be raised by renal tubular acidosis or severe urinary tract infections with proteus bacteria.

Caution is recommended in patients with epilepsy. Lowering of seizure threshold has been observed in isolated cases. Patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III – IV) and uncontrolled hypertension should be closely supervised due to lack of data in these conditions [2].

Memantine has the potential to interact with a number of drugs (see SPC for full details). Its mode of action suggests that memantine may enhance the effects of L-dopa, dopaminergic agonists and anticholinergics. Memantine may reduce the effects of barbiturates and neuroleptics. Drugs using the same renal transport system as memantine may also interact leading to a potential risk of increased plasma levels (i.e. cimetidine, ranitidine, procainamide, quinine and nicotine). Concurrent use of NMDA antagonists should be avoided e.g. amantadine, ketamine, dextromethorphan. Since these drugs act at the same receptor as memantine there is a possibility of increased side effects (mainly CNS).

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Table 2: RCTs of memantine in AD and VaD

Ref No	Design of Study (Publication Type)	Treatments Assessed	Primary Outcome Measures	Results and Comments
Reisberg B et al Pivotal trial USA [6]	28 week randomised, double blind, placebo-controlled, phase III, parallel group multicentre trial.  Assessing memantine in moderately severe to severe AD	Memantine 10mg bd vs. placebo n=252 (mean age 76yrs) Outpatients with moderately severe to severe AD MMSE 3-14 GDS 5 or 6	- CIBIC-plus (clinical global change) - Functional domain using ADCS-ADLsev (activities of daily living)  Secondary endpoint – cognition using SIB	181 completers – dropout rate of 28% The results favoured memantine over placebo. ITT-LOCF population: - CIBIC-plus, mean difference 0.3 points (p=0.06; 95%CI –0.05,0.02) - ADL total score, mean difference 2.1 points (p=0.02; 95%CI 0.49,3.78) - SIB total scores, mean difference 6.1 points (p=0<0.001; CI not stated) Memantine was safe and well tolerated.
9MBEST Latvia [9]	12 week, randomised, double-blind, multicentre, placebo-controlled, phase III trial  Safety and efficacy in moderately severe to severe dementia (AD and VaD)	Memantine 10mg od vs. placebo n=166 Care dependent in-patients with moderately severe to severe dementia (49% AD, 51% VaD) GDS stages 5-7 MMSE <10	- CGI-C rated by physician - BGP, sub score care dependence, rated by nursing staff  Secondary endpoint – D-scale	166 pts entered ITT analysis - Positive response in CGI-C seen in 73% v 45% in favour of memantine (stratified Wilcoxon p<0.001) independent of aetiology of dementia. - BGP subscore 3.1 points improvement (memantine) & 1.1 points (placebo) p=0.016 - Secondary endpoint analysis of the D-scale support the primary results No significant differences regarding safety observed between groups
MMM 300 France [13] - *	28 week randomised, placebo-controlled, phase III, multicentre, double-blind, parallel trial  Safety & efficacy of memantine in mild to moderate VaD	Memantine 20mg/day vs. placebo. n=321 Outpatients with probable VaD (defined by NINDS-AIREN criteria and a MIS) and MMSE 12-20	- cognitive subscale of ADAS-cog (cognitive assessment) - CIBIC-plus (global rating of change)	288 pts valid for ITT analysis - mean ADAS-cog scores significantly improved with memantine relative to placebo. Memantine grp mean score gained average 0.4 points, placebo mean score declined 1.6 pts i.e. a difference of 2.0 pts (95% CI: 0.49,3.60) - Response rate for CIBIC-plus was 60% with memantine vs. 52% with placebo but the difference was non-significant. Memantine was well tolerated with an adverse event rate comparable to placebo.
MMM500 UK [14] - *	28 week, double-blind, parallel, randomised, placebo controlled, multicentre, phase III trial  Safety and efficacy in mild to moderate VaD	Memantine 10mg bd vs. placebo n=579 Outpatients with probable VaD (based on DSM-III-R & NIMDS-AIREN criteria) MMSE 10-22	- ADAS-cog - CGI-C	548 pts with at least 1 post baseline efficacy assessment entered ITT analysis - mean ADAS-cog scores differed by 1.75 points in favour of memantine (95% CI: -3.023, -0.49) - CGI-C ratings NS Memantine was well tolerated. Dizziness was most frequent adverse effect (10% memantine, 4% placebo)
<b>Combination Therapy</b>				
Tariot P et al US [12]	24 week double blind, parallel group, placebo-controlled, randomised, multicentre trial  Safety & efficacy of memantine in pts with moderate to severe AD maintained on the cholinesterase inhibitor, donepezil	Memantine 20mg/d + donepezil 5 or 10mg/d v placebo + donepezil 5 or 10mg/d n = 403 Outpatients with AD (NINCDS – ADRDA criteria) MMSE 5-14 Mean age 76yrs	- Cognition: SIB - Function: ADCS-ADL  Secondary endpoint – Global: CIBIC-plus	Not published 395 pts valid for ITT analyses - Cognition: statistically significant improvement in combination group as measured by SIB p=0.0001 - Function: combination group showed significantly less decline in function as measured by ADCS-ADL p=0.028 - Global status: combination group statistically significant global improvement as measured by CIBIC-plus p=0.027  Adverse event rates similar for pts in the two treatment groups. NB. Will statistically significant differences translate into clinically significant ones?

\* Unlicensed indication

GDS: Global Deterioration Scale, score range 1(no dementia) to 7(very severe dementia).

NINDS-AIREN: National Institute of Neurological Disorders & the Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

NINCDS-ADRDA: National Institute of Neurologic, Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association.

DSM: Diagnostic and Statistical Manual of Mental Disorders.

For all other abbreviations see table 1.