London, 15 November 2005
Product name: Ebixa
Procedure number: EMEA/H/C/463/II/15

SCIENTIFIC DISCUSSION

1. INTRODUCTION

This variation concerns an extension of the approved indication for memantine to include the treatment of moderate to moderately severe Alzheimer's disease (AD). Originally, memantine was approved in Europe for the treatment of moderately severe to severe AD.

AD characteristics

AD is a chronic illness with progressive neurodegeneration and dementia. The cause of the disease remains unknown. Its diagnosis is an exclusion diagnosis in the face of a dementia with insidious onset, a gradual progression, and no sign of another cause of dementia. The neuropathology of AD is characterised by extensive neuronal cell loss, deposition of numerous senile plaques and neurofibrillary tangles in the cerebral cortex.

There is a trend for the prevalence of AD to increase exponentially with age; above the age of 60 years, the prevalence approximately doubles with every 4.5 years. AD has been estimated to affect approximately 1% of the population aged between 65 and 69 years, and up to more than 20% of those aged above 85 years. According to a recent study, the prevalence of AD in Europe in the year 2000 was 4.7 million.

AD is the most common form of dementia and is estimated to account for some 60 to 70% of cases. For some patients, AD progresses rapidly over the 2 to 3 years following diagnosis, but for most the decline in cognitive and functional abilities is more gradual and occurs over approximately 7 years. The majority of patients with AD are in the mild to moderate range of the disease, as it has been estimated that approximately one-third of patients have mild AD, one-third have moderate AD, and one-third have severe AD.

AD current treatment

The treatment of AD should ideally improve the global condition of the patient by seeking to:

- improve or at least slow the loss of memory and cognition
- help maintain independent function
- control the behavioural symptoms associated with the disease

At present, the only treatments approved in Europe for mild to moderate AD are three acetylcholinesterase inhibitors (AChEIs). These drugs augment cholinergic neurotransmission, since loss of acetylcholine occurs early and correlates with impairment of memory.

Memantine acts on the glutamatergic system via antagonism of the NMDA receptor. It was approved in Europe in May 2002 and remains the only drug licensed in Europe for moderately severe to severe AD.

Memantine properties

Glutamate is an excitatory neurotransmitter in cortical and hippocampal neurons. There is increasing evidence that disturbed glutamatergic neurotransmission could be involved in AD pathology, and this may occur already in the early stages of the disease.

Anatomical and biochemical evidence suggests that there is both pre- and postsynaptic disruption of Excitatory Amino Acids (EAA) pathways in Alzheimer's disease. Dysfunction of EAA pathways could play a role in the clinical manifestations of Alzheimer's disease, such as memory loss and signs of cortical disconnection. Furthermore, EAA might be involved in the pathogenesis of Alzheimer's disease, by virtue of their neurotoxic (excitotoxic) properties. Circumstantial evidence raises the possibility that the EAA system may partially determine the distribution of pathology in Alzheimer's disease and may be important in producing the neurofibrillary tangles, RNA reductions and dendritic changes which characterize this devastating disorder.

Memantine can interact with a variety of ligand-gated ion channels. However, NMDA receptors appear to be a key target of memantine at therapeutic concentrations. Blockade of NMDA receptors by memantine could theoretically confer disease-modifying activity in AD by inhibiting the "weak" NMDA receptor-dependent excitotoxicity that has been hypothesized to play a role in the progressive neuronal loss that underlies the evolving dementia. Moreover, recent *in vitro* studies suggest that memantine abrogates beta-amyloid toxicity and possibly inhibits beta-amyloid production. Considerable attention has focused on the investigation of theories to explain the better tolerability of memantine over other NMDA receptor antagonists, particularly those that act by a similar channel blocking mechanism such as dissociative anaesthetic-like agents. A variety of channel-level factors could be relevant, including fast channel-blocking kinetics and strong voltage-dependence (allowing rapid relief of block during synaptic activity), as well as reduced trapping (permitting egress from closed channels). These factors may allow memantine to block channel activity induced by low, tonic levels of glutamate, an action that might contribute to symptomatic improvement and could theoretically protect against weak excitotoxicity while sparing synaptic responses required for normal behavioural functioning, cognition and memory.

2. CLINICAL ASPECTS

2.1 CLINICAL EFFICACY DATA

The MAH applied for an extension of the indication to include the monotherapy treatment of patients with mild to moderate Alzheimer's disease. The basis for this application consisted of two placebo controlled studies with comparable designs and similar populations.

Both studies were conducted in accordance with the version of the Declaration of Helsinki and the principles of Good Clinical Practice applicable at the time.

Main studies - Studies MD-10 and 99679

Studies MD-10 and 99679 were multi-centre, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose studies of essentially identical design (Table 1).

Table 1 Overview of Clinical Monotherapy Studies in Mild to Moderate AD

Study ID	Study Design and Duration	Number of Randomised Patients	
		PBO	MEM
MD-10	24-week, double-blind, PBO-controlled, fixed-dose study with a 1:1 randomisation of MEM to PBO	202	201
99679	24-week, double-blind, PBO-controlled, fixed-dose study with a 2:1 randomisation of MEM to PBO	152	318
Pooled analysis	Comprised data from Studies MD-10 and 99679	354	519

Both studies are being followed by long-term open-label extension studies that are investigating memantine treatment over 2½ to 3 years (Studies MD-11 and 99819, respectively). These extension studies are currently ongoing.

Design and Methods

In Study MD-10, there was a 1- to 2-week single-blind placebo run-in period, after which patients were randomised in a 1:1 ratio of memantine to placebo to 4 weeks of up-titration followed by 20 weeks of double-blind maintenance treatment with memantine 20mg/day (10mg twice daily) or placebo. In Study 99679, there was a 1- to 2-week screening period, after which patients were randomised in a 2:1 ratio of memantine to placebo to 4 weeks of up-titration followed by 20 weeks of double-blind maintenance treatment with memantine 20mg/day (10 mg twice daily) or placebo.

Study population

Both studies included outpatients of either sex, aged above 50 years, with a primary diagnosis of probable AD using National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Study 99679 used DSM-IV-TR criteria for Dementia of the Alzheimer's type as an additional diagnostic tool.

Further selection criteria included a Mini Mental State Examination (MMSE) score ≥10 and ≤22 (Study MD-10) or ≥11 and ≤23 (Study 99679), a Modified HIS ≤4, and the diagnosis of probable AD consistent with the result of a CT or MRI performed within the past 12 months. Study MD-10 also required a Montgomery-Åsberg Depression Rating Scale (MADRS) score <22 at Screening. Any patients who had previously been treated with AChEIs were to have stopped such treatment at least 30 days prior to inclusion in the study.

Outcome Measures

The primary efficacy variables were the change from Baseline to Week 24 in the ADAS-cog total score and the CIBIC-plus rating score.

Secondary efficacy measures included:

- ADAS-cog total score by visit
- CIBIC-plus score by visit
- Mean change from baseline in ADCS-ADL score by visit
- Mean change from baseline in NPI score by visit

Additional analyses were performed on the proportions of responders (marked improvement in the cognitive domain [ADAS-cog improvement ≥4] and improvement or stabilisation in the global domain [CIBIC-plus ≤4]).

Safety evaluations were based on adverse events, clinical safety laboratory tests, ECGs, vital signs, and physical examinations.

Clinical assessments were performed at Baseline and at Weeks 4, 12, 18, and 24. Study MD-10 had an additional clinical assessment at Week 8.

Statistical analysis

In Study MD-10, the primary efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomised patients who took at least one dose of double-blind study product and who had at least one valid post-baseline measurement of one of the primary efficacy parameters. The last observation carried forward (LOCF) approach for imputation of missing data was used in the primary analysis of the efficacy variables. All the secondary efficacy analyses were performed on the ITT population using both the LOCF and the observed case (OC) approach.

In Study 99679, the primary efficacy analyses were performed on the completers set at Week 24 (CS24), defined as all patients in the full-analysis set (FAS) who took study product up to Week 24 and who were assessed on both primary efficacy parameters at the Week 24 visit. The FAS was defined as all randomised patients who took at least one dose of double-blind study product and who had at least one valid post-baseline assessment of both primary efficacy parameters. All the secondary analyses were performed on the CS24, and on the FAS (LOCF and OC).

In both studies, the analysis of ADAS-cog was based on an analysis of covariance (ANCOVA) with factors for treatment group and centre, and with the baseline score as a covariate. In Study MD-10, the primary analysis of CIBIC-plus was based on the Cochran-Mantel-Haenszel (CMH) test stratifying by centre. In Study 99679, the primary analysis of CIBIC-plus was based on an ANCOVA. The same ANCOVA model was used for all analyses of change from baseline to Week 24 in the secondary efficacy parameters.

All estimated differences between memantine and placebo were based on least square mean (LS mean) for changes from baseline. The proportions of responders were analysed by visit using Fisher's exact test.

Results

Study MD-10

The study was conducted in 42 sites in US from October 01 to July 03. A total of 403 patients were randomised to the two treatment groups: 201 to the memantine group and 202 to the placebo group. Of these, 332 (82%) patients completed the study: 165 (82%) in the memantine group and 167 (83%) in the placebo group. The most frequent reason for discontinuation was adverse event, reported by 5.0% of placebo-treated patients and 9.5% of memantine-treated patients. The ITT population comprised 394 patients: 196 in the memantine group and 198 in the placebo group

Approximately 40% of the patients were men and the mean age was 77.5 years [range: 51 to 95 years]. The majority (91%) of the patients were Caucasian. The mean baseline MMSE total score was 17.3 [range: 10 to 24]. There were no statistically significant differences between treatment groups with respect to any of the demographic and baseline characteristics.

Prior use of anti-dementia medications was similar in the placebo-treated and memantine-treated groups (approximately 69% and 62%, respectively). Prior use of the AChEI medications used to treat dementia was similar in both the memantine-treated and placebo-treated groups: donepezil (55% vs. 56%), rivastigmine (18% vs. 25%) and galantamine (14% vs.18%), respectively.

The mean exposure to study product was 150 days in the memantine group and 151 days in the placebo group. The overall mean daily dose for the memantine-treated group was 17.9 mg.

ADAS-cog Total Score

In the primary efficacy analysis, at Week 24, the mean change from baseline in the ADAS-cog total score was –0.8 for the memantine group, compared to 1.1 for the placebo group. The mean difference of –1.9 between the two groups was statistically significant in favour of memantine (p=0.003). Statistically significant differences in favour of memantine were also observed at Weeks 8, 12, and 18. Throughout the study, the memantine-treated patients showed improvement on the ADAS-cog, while after Week 4, the placebo-treated patients showed deterioration.

The results of the secondary OC analysis resembled those of the LOCF analysis, although statistical significance was not achieved at Week 24 (p=0.13). There were 71 patients included in the LOCF analysis of the ADAS-cog who were not included in the corresponding OC analysis. For this group, the LS mean change from Baseline in the ADAS-cog was -2.2 for the memantine-treated group, compared to 1.5 for the placebo-treated group. The LS mean difference of -3.7 between the two groups was statistically significant in favour of memantine (p=0.044). Thus, a greater number of memantine-treated patients were improving at the time of their discontinuation than the placebo-treated patients (p=0.001).

A *post hoc* sensitivity analysis, using the mixed-model repeated-measured supported the LOCF analysis (p=0.013).

CIBIC-plus Total Score

The mean CIBIC-plus total score at Week 24 was 4.2 for memantine-treated patients compared to 4.5 for placebo-treated patients. This difference was statistically significant (p=0.004) in favour of memantine.

The results of the secondary OC analysis at Week 24 were consistent with those of the LOCF analysis. The mean CIBIC-plus scores at Week 24 was 4.2 for memantine-treated patients compared to 4.5 for placebo-treated patients (p=0.030).

Secondary Efficacy Analysis

The ADCS-ADL (activities of daily living) showed no significant difference between memantine treatment and placebo treatment.

On the NPI there was statistically significant benefit of memantine treatment compared to placebo treatment (p=0.035 at Week 12 and p=0.011 at Week 24, LOCF).

Study 99679

This clinical trial was conducted on 65 study sites in Europe from May 02 to September 03. A total of 470 patients were randomised to the two treatment groups: 318 to the memantine group and 152 to the placebo group. Of these, 409 (87%) patients completed the study: 271 (85%) in the memantine group and 138 (91%) in the placebo group. The most common primary reasons for withdrawal was adverse events (9% in the memantine group versus 4% in the placebo group).

Approximately 40% of the patients were men and the mean age was 73.4 years [range: 54 to 89 years]. All the patients were Caucasian. There was no statistically significant difference between the memantine and the placebo groups in any of the measured baseline values. The baseline MMSE scores indicate a population with mild to moderate AD with a somewhat skewed distribution towards those more mild patients. The mean baseline MMSE total score was 18.7 [range: 11 to 23]

Regarding recent dementia medication taken by memantine-treated patients, 38% of the memantine-treated patients and 36% of the placebo-treated patients had been treated with an AChEI prior to being enrolled in the study.

The mean exposure to study product was 156 days in the memantine group and 162 days in the placebo group.

ADAS-cog Total Score

In the pre-defined primary analysis at Week 24, the difference favouring memantine over placebo was not statistically significant, although the memantine-treated patients had a mean improvement of 1.93 points at Week 24 compared to their baseline ADAS-cog total score (CS24).

Cognitive functioning, measured by the ADAS-cog total score, improved from baseline to Week 4 in both treatment groups. From Week 4, the treatment groups separated and the patients receiving memantine were statistically significantly better than those receiving placebo at Weeks 12 and 18 ($p<0.001$ and p=0.016, respectively).

Overall, cognitive functioning in the placebo-treated patients did not deteriorate as expected from previous trial data in this population; instead, the placebo-treated patients had an improved ADAS-cog total score at Week 24 compared to baseline. Similar results were found using the LOCF approach.

CIBIC-plus Total Scores

At the pre-defined primary analysis at Week 24, the difference favouring memantine over placebo was not statistically significant. Memantine separated early from placebo and the difference was statistically significant in favour of memantine at Weeks 12 and 18 (p=0.033 at Week 12 and p=0.012 at Week 18). In the memantine group, the CIBIC-plus scores at Week 24 were slightly improved relative to those at baseline. In the placebo group, the CIBIC-plus scores deteriorated from Weeks 4 to 18 and improved unexpectedly from Weeks 18 to 24. Similar results were found using the LOCF approach.

Secondary Efficacy Analyses

On the secondary efficacy scales the ADCS-ADL and the NPI, no statistically significant differences between memantine and placebo were seen. The baseline level of behavioural neuropsychiatric symptoms was low.

Analysis performed across trials (pooled analyses)

The similarity of the designs and conduct of Studies MD-10 and 99679 allowed the two studies to be pooled to increase the power of the analyses.

In the pooled data set, the efficacy analyses were performed on the FAS. The pooled FAS comprised the ITT population from Study MD-10 and the FAS from Study 99679. All analyses were performed on both LOCF and OC.

The pooled analysis of ADAS-cog was based on an ANCOVA and the non-parametric Kruskal-Wallis test. The pooled analysis of CIBIC-plus was based on an ANCOVA and CMH. The ANCOVA was performed with treatment and centre as factors, and the relevant baseline score as a covariate. Responder analyses were based on Fisher's exact test.

The pooled data set comprised 873 patients: 519 in the memantine group and 354 in the placebo group. Of these, 741 (85%) patients completed the studies: 436 (84%) in the memantine group and 305 (86%) in the placebo group. The FAS comprised 855 patients: 506 in the memantine group and 349 in the placebo group.

Approximately 40% of the patients were men and the mean age was 75.5 years [range: 51 to 95 years]. The majority (96%) of the patients were Caucasian. The mean baseline MMSE total score was 18.1. There was no statistically significant difference between the memantine and the placebo group in any of the measured baseline values. The mean exposure to study product was 154 days in the memantine group and 156 days in the placebo group.

ADAS-cog Total Score

Using parametric methods (ANCOVA), memantine was statistically significantly better than placebo from Week 12 onwards. At Week 24, the treatment difference to placebo was statistically significant in the LOCF ($p=0.004$) and OC analyses ($p=0.049$).

CIBIC-plus Total Score

The treatment difference to placebo for CIBIC-plus was also statistically significant in the LOCF ($p=0.022$) and OC analyses ($p=0.047$) (ANCOVA).

The pooled data were also re-analysed using non-parametric methods (Kruskal-Wallis and CMH on the ADAS-cog and CIBIC-plus, respectively) to verify the robustness and consistency of the results. Regardless of whether parametric or non-parametric methods were used, statistically significant separation of memantine from placebo at Weeks 12, 18 and 24 on both primary efficacy scales in the LOCF and OC analyses was demonstrated.

Other Efficacy Analyses

There was no statistically significant difference between memantine and placebo on the ADSC-ADL.

In the pooled analysis, the memantine group showed numerical improvement relative to the placebo group on the NPI at both Weeks 12 and 24 (LOCF), and the difference was statistically significant at Week 12 ($p=0.03$). The baseline level of behavioural neuropsychiatric symptoms was low in both studies.

Responder Analyses

The proportion of memantine-treated patients who responded was statistically significantly superior to that of placebo-treated patients from Week 12 onwards, based on the dual criterion with ADAS-cog and CIBIC-plus (ADAS-cog improvement ≥ 4 and CIBIC-plus ≤ 4) and on the single criterion (ADAS-cog improvement ≥ 4 or CIBIC-plus ≤ 4). The results were similar for FAS, OC.

2.2 EFFICACY ASSESSMENT

Two studies (MD-10 and 99679) in which patients with mild to moderate Alzheimer's disease had been enrolled formed the basis for efficacy of the initial variation application.
The CHMP considered that the design of the studies, the qualification of the patients and the selected outcome measures fulfil the standard requirements of the disease and the AD guidelines. However, when the clinical trials were conducted (from 2001 to 2003), there were available antidementia products approved for the same population that memantine is focused on. The MAH stated in their application that there is no reference drug that consistently and to a large extent improves patients with AD. However, the CHMP considered that a three-arm design including an active comparator and a placebo arm could have been of value.

Different primary efficacy populations were considered in each study. In Study MD-10 the primary efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomised patients who took at least one dose of double-blind study product and who had at least one valid post-baseline measurement of one of the primary efficacy parameters. The last observation carried forward (LOCF) approach was used for imputation of missing data.

In Study 99679, the primary efficacy analyses were performed on the completers set at Week 24 (CS24), defined as all patients in the full-analysis set (FAS) who took study product up to Week 24 and who were assessed on both primary efficacy parameters at the Week 24 visit. The FAS was defined as all randomised patients who took at least one dose of double-blind study product and who had at least one valid post-baseline assessment of both primary efficacy parameters.

The MAH provided an analysis in which the populations of both studies are pooled together in order "to increase the power of the analyses". For Study 99679, the pooled data set population is not the same as the primary efficacy population considered in the main study (CS24 for primary analysis, FAS for being pooled). In any case, neither of them represents a "true ITT population". The MAH was requested to provide a new analysis based on more strict criteria including all randomised patients.
In Study MD-10, for the ADAS-cog analysis, the difference in number of all randomised patients and the IIT population was 4 placebo and 5 memantine treated patients. The results of the corresponding efficacy analyses were essentially the same, and both results were statistically significant. For the CIBIC-plus, the difference between all randomised patients and the ITT was 5 patients in each treatment arms, and the corresponding efficacy analyses were similar and statistically significant in favour of memantine. Also, in Study 99679 there were small differences in the number of patients in each treatment arm between the FAS (LOCF) and the all randomised patients, but these had negligible impact on the treatment differences and no impact on the statistical significances.

The CHMP was also of the opinion that the use of the OC without imputation of missing data is usually considered as a conservative approach for the evaluation of the efficacy of treatments for degenerative diseases.
The MAH clarified that in Study MD-10, the primary efficacy analysis was LOCF analysis of the ITT population. The MAH showed that there were no large differences in the withdrawal rates in the two arms of Study MD-10 (18% in the memantine group, 17% in the placebo group), nor in the pattern of withdrawals over time, therefore differential withdrawal would not be an influencing factor in the LOCF analysis in Study MD-10.
The CHMP acknowledge that since the dropouts were fairly distributed there was a smaller risk of having a biased LOCF.

Pre-treated AChEI patients were allowed to be enrolled in the studies. A carry over effect cannot be excluded in spite of the pre-defined 30-day washout period. Taking into account the post-treatment effect for some of the marketed AChEIs, the MAH was requested to provide some clarifications.
The MAH provided information on the possible influence of the pre-treatment of the patients on the results. The time interval between previous treatment and study treatment was equally balanced between the placebo and memantine groups within both studies.

Thus, the influence of any potential carry-over effect should have been the same in the placebo and memantine groups. Moreover, the majority of the previously treated patients stopped AChEI treatment more than 2 months before enrolment in the memantine studies.

In the primary efficacy analysis of Study MD-10, at Week 24, the mean difference change from baseline between the two groups in the ADAS-cog total score was –1.9 (–0.8 for the memantine group, compared to 1.1 for the placebo group; p=0.003). Throughout the study, the memantine-treated patients showed improvement on the ADAS-cog, while after Week 4, the placebo-treated patients showed deterioration. The results of the secondary OC analysis resembled those of the LOCF analysis, although statistical significance was not achieved at Week 24 (p=0.13).
The mean CIBIC-plus total score at Week 24 was 4.2 for memantine-treated patients compared to 4.5 for placebo-treated patients. This difference was statistically significant (p=0.004) in favour of memantine. The results of the secondary OC analysis at Week 24 were consistent with those of the LOCF analysis. In summary, the study MD-10 was positive. There was a clinical response in the two primary variables. The size of the effect, as compared to the placebo effect is, however, small but apparently similar to that obtained with AChEIs.

In Study 99679 the two co-primary variables did not reach statistical significance at the pre-defined primary analysis (CS24) at Week 24. At that point for cognitive functioning (ADAS-cog), the mean change difference between groups was 0.85 in favour of memantine (p=0.156). For global functioning (CIBIC-plus), the difference in favour of memantine was 0.07 (p=0.523).

The MAH proposed that the difference of memantine over placebo was smaller than expected because the response to placebo was higher than anticipated. From the data provided, the placebo behaves in a very atypical way. At Week 12, placebo patients stopped deteriorating and improved ADAS-cog in a way that would be even compatible with concomitant active treatment. The MAH was asked to provide evidence that concomitant active anti-dementia treatment has not occurred in the trial.
The MAH investigated a number of different issues in order to try to understand the placebo response in Study 99679 (blinding, quality control of study product, vascular co-morbidity, previous treatment with AChEIs, concomitant treatment with potential anti-dementia drugs, predictive factors, treatment-by-centre interaction) but none of the analyses or considerations could satisfactorily explain the unusual placebo response towards the end of the study.

The main interest of this clinical development is focused on the efficacy of memantine in patients with mild to moderate dementia. Mean baseline MMSE total score of the studies reflects a moderate population. Study 99679 included a greater proportion of mild dementia patients than Study MD-10.
Some *post hoc* analyses of the primary and pooled analyses suggested a better effect in patients with more severe AD and in patients who had previously used AChEIs. The MAH was asked to provide the baseline characteristics of the population contained in the pooled data set and its distributions and particularly an analysis of the effect of memantine on this mild population.
The MAH provided the distribution of the patients enrolled in the two studies according to the baseline severity. A total of 30% (n=58) of patients in Study MD-10 and 50% (n=75) of patients in Study 99679 receiving placebo were mild (identified by MMSE≥20). Regarding the active groups, 36% (n=70) and 46.5% (n=144), respectively, of patients treated with memantine were mild.

The MAH also provided a subgroup analysis on mild patients versus all patients and versus moderate patients in study MEM-MD-10. The treatment difference throughout the study was nearly similar in the mild patients when compared to all patients, both for ADAS-cog and CIBIC-plus. These differences did not reach statistical significance at endpoint due to the decreased number of patients included in this sub-analysis.

The CHMP considered that this relevant subgroup was properly represented in the whole population involved in the clinical trials, however, patients with milder forms contribute less to the differences versus placebo than the patients with moderate disease.

To further illustrate the clinical relevance of memantine's effects, the MAH provided responder analyses. Considering Studies MD-10 and 99679 individually, neither were deliberately designed (powered) to show a statistically significant difference with regards to responder analyses. However, in both studies statistically significant differences were observed at various time points using a dual-responder criterion (an improvement of 4 points or more in ADAS-cog total score and improvement or stabilisation in CIBIC-plus (CIBIC-plus ≤4 points). In Study MD-10, statistically significant differences were observed at Weeks 8, 12, and 18. In Study 99679, statistically significant differences were observed at Weeks 12 and 18.
In the pooled analysis, the memantine group had statistically significant more responders at endpoint (Week 24). Furthermore, statistical significance was achieved at Weeks 12 and 18. This demonstrates the overall benefit of the effect seen on the primary endpoints.

In addition, the CHMP requested a responder analysis taking the ADAS-cog, CIBIC-plus and ADL into account. The MAH performed a responder analysis defined as at least 4 points improvement in ADAS-cog and improvement or stabilisation in CIBIC-plus or ADCS-ADL score. In the pooled analysis, the memantine group had statistically significantly more responders at both Weeks 12 and 24.

Meta analysis on all phase III, placebo controlled, 6-month studies

The CHMP requested additional studies within the target population to be submitted. Therefore the MAH included meta-analyses and responder analyses conducted on all phase III, placebo-controlled, 6-months studies with memantine in mild to severe AD (see Table 2).

Table 2 Phase III, Placebo-controlled, 6-month Clinical Studies in AD

Study No. Sponsor[a]	MMSE Inclusion Range (Mean[b])	Duration / Design	Number of Treated Patients	Key Efficacy Parameters
MD-10 * Forest	10 – 22 (17.3)	24-week / DB, PBO-controlled	403 PBO: 202 MEM: 201	ADAS-cog CIBIC-plus $ADCS\text{-}ADL_{23}$ NPI
MD-12 Forest	10 – 22 (16.9)	24-week / DB, PBO-controlled in patients already receiving donepezil, rivastigmine, or galantamine	433 PBO: 216 MEM: 217	ADAS-cog CIBIC-plus $ADCS\text{-}ADL_{23}$ NPI
99679 * Lundbeck	11 – 23 (18.7)	24-week / DB, PBO-controlled	470 PBO: 152 MEM: 318	ADAS-cog CIBIC-plus $ADCS\text{-}ADL_{23}$ NPI
MD-01 Forest	5 – 14 (10.1)	24-week / DB, PBO-controlled	350 PBO: 172 MEM: 178	SIB CIBIC-plus $ADCS\text{-}ADL_{19}$ NPI
MD-02 Forest	5 – 14 (10.0)	24-week / DB, PBO-controlled in patients already receiving donepezil	403 PBO: 201 MEM: 202	SIB CIBIC-plus $ADCS\text{-}ADL_{19}$ NPI
MRZ-9605 ** Merz	3 – 14 (7.7)	28-week / DB, PBO-controlled	252 PBO: 126 MEM: 126	SIB CIBIC-plus $ADCS\text{-}ADL_{19}$ NPI

DB, double blind; MEM, memantine; PBO, placebo
* Previously submitted as part of the initial type II variation application for mild to moderate AD
** Previously submitted as part of the original MAA
[a] Merz Pharmaceuticals GmbH; Forest Laboratories, Inc.; H. Lundbeck A/S
[b] All Patients Treated Set

The MAH acknowledged the CHMP's concern that the treatment effect was smaller in the milder patients and proposed to restrict the applied-for indication to treatment of *moderate to severe AD* (baseline MMSE score of ≤19). This extends the current indication less than originally intended by the MAH. The MAH provided additional data (a meta-analyses and a responders analysis) that documented the beneficial effect of memantine in this population:

- The meta-analyses on the efficacy endpoints showed statistically significant and clinically relevant effects of memantine compared to placebo on the cognitive ($p<0.001$), global ($p<0.001$), and functional domains ($p<0.01$)(LOCF and OC), with effect sizes in the same range as AChEIs
- The triple responder analyses were performed based on definitions that identified patients whose condition concurrently worsened in all three domains during the 6-month treatment:
    - Marked Clinical Worsening – a decline of ≥4 points on the ADAS-cog or ≥5 points on the SIB and a decline on the CIBIC-plus and a decline on the ADL
    - Any Clinical Worsening – any decline on the ADAS-cog or on the SIB and any decline on the CIBIC-plus and any decline on the ADL

In patients identified with concurrent worsening in all three domains, memantine had a statistically significant effect in preventing worsening, as twice as many placebo-treated patients as memantine-treated patients showed marked clinical worsening in all three domains (21% vs. 11%, $p<0.0001$).

The analyses of *Any Clinical Worsening* showed similar results and the analyses were statistically significant using both OC and LOCF.
The CHMP considered that the additional data supported the new proposed modified indication. The wording is also consistent with that of the approved indication in other regions (US).

2.3 CLINICAL SAFETY

The safety evaluation of memantine in the treatment of mild to severe AD was based on data from six 6-month, placebo-controlled clinical studies, one 3-month, placebo-controlled study in institutionalised patients with severe AD or VaD and two 6-month, placebo-controlled studies in mild to moderate Vascular Dementia. These data were supported by 28-week interim safety results from the ongoing, open-label, long-term Study 99819 (extension of Study 99679), with a cut-off date of 31 December 2003, which includes 1-year exposure data in mild to moderate AD. A total of 1784 patients were exposed to memantine in the placebo-controlled studies, and 159 mild to moderate AD patients were included, who had been exposed to memantine for 1 year.

Study MD-11 is an ongoing long-term (132-week) extension of Study MD-10. An interim analysis of this study has not been performed and, therefore, only essential information (recruitment, deaths, and other serious adverse events (SAEs) are provided in this summary.

Safety Analysis Data Sets

The populations that were used for the safety analyses are defined below.

- *Current SPC Population*, comprises the patients with moderately severe to severe dementia (MMSE score <15), from placebo-controlled Studies 9202, 9403, 9408, and 9605.
- *Overall Safety Population*. To allow an overall evaluation of Treatment-Emergent Adverse Events (TEAEs), the data from the all placebo-controlled AD and VaD studies have been merged to form the overall safety population. All patients who took at least one dose of double-blind study product (the all patients treated set, APTS) were included in this population.
- *Study 99819 Interim Safety Population,* includes interim safety data from Study 99819 for patients who, as of 31 December 2003, had either completed the Week 28 visit or had withdrawn from study. For patients who as of the cut-off date had completed the Week 28 visit, data for the first 28 weeks of open-label treatment are included.
- *One-year Exposure Safety Population*. The one-year exposure safety population includes safety data from Studies 99679 and 99819 for all patients who had been treated with memantine for 1 year as of the cut-off date of 31 December 2003. In the analysis based on this population, the start of Study 99679 has been used as the baseline.

Patient exposure

A total of 3379 patients with mild to severe dementia, were included in this analysis. In the overall safety population, 1784 patients received memantine and the total exposure was 749 years and mean exposure was 154 days. In the Study 99819 interim safety population (with a cut-off date of 31 December 2003), 273 of the 353 enrolled patients were included, 92 of whom had been treated with placebo in Study 99679. As of 31 December 2003, a total of 159 patients had been treated with memantine for 1 year (from Studies 99679 and 99819).

In Study MD-11, as of 31 March 2004, 314 patients had been randomised and treated with memantine for an additional 28 weeks, 236 of whom had continued treatment with memantine for another year, 34 of whom had continued treatment with memantine for a third year.

Adverse events

Treatment-emergent Adverse Events

Overall Safety Population

Approximately 70% of the patients had TEAEs and the proportion of memantine-treated patients with TEAEs was similar to that of placebo-treated patients. The proportion of patients in the memantine group who had at least one SAE was slightly lower in the memantine group than that in the placebo group (12.7% *versus* 13.8%). The incidence of withdrawal due to adverse events was low and the same in both treatment groups (10%).

TEAEs with an incidence ≥4% in any treatment group are presented in Table 4. Only small differences between treatment groups were observed.

Table 4 TEAEs with an Incidence ≥4% in Either Treatment Group

	PBO		MEM	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients Treated	1595		1784	
Patients with Treatment Emergent Adverse Events	1122	(70.3)	1246	(69.8)
Agitation	158	(9.9)	114	(6.4)
Dizziness	89	(5.6)	113	(6.3)
Accidental injury	111	(7.0)	101	(5.7)
Fall	99	(6.2)	99	(5.5)
Headache	62	(3.9)	92	(5.2)
Confusion	65	(4.1)	84	(4.7)
Constipation	41	(2.6)	82	(4.6)
Diarrhoea	74	(4.6)	78	(4.4)
Influenza-like symptoms	63	(3.9)	74	(4.1)
Hypertension	42	(2.6)	71	(4.0)
Urinary tract infection	66	(4.1)	63	(3.5)
Insomnia	71	(4.5)	54	(3.0)

Deaths

Overall Safety Population

During double-blind treatment or within 30 days after the last dose, 48 of the 1784 patients treated with memantine and 45 of the 1595 patients treated with placebo died.

The causes of death were not different from what can be expected in an elderly population and were of a cardiovascular or respiratory nature. In both treatment groups, all SAEs that resulted in death were considered *not related* to study product by the investigator.

Study 99819

As of 15 May 2004 (the cut-off date for the most recent PSUR), 7 of the 353 patients in ongoing extension Study 99819 had died during open-label treatment or within 30 days after the last dose. Two patients died more than 30 days after their last dose of study product. The causes of death were not

different from what can be expected in an elderly population and were typically of a cardiovascular, respiratory, or cancer-related nature. All SAEs that resulted in death were considered *not related* to study product by the investigator.

Study MD-11
As of 31 March 2004, 17 of the 314 patients in ongoing long-term extension Study MD-11 had died. All SAEs that resulted in death were considered *not related* to study product by the investigator. Except for deaths caused by AD, the pattern of SAEs that resulted in death in this ongoing extension study was not different from that in the completed, double-blind, placebo-controlled studies in mild to moderate AD.

Serious Adverse Events

Overall Safety Population
A total of 226 (12.7%) memantine-treated patients and 220 (13.8%) placebo-treated patients in the *overall safety population* had at least one SAE (including deaths) during double-blind treatment or within 30 days after the last dose.
Overall, the pattern and incidences of SAEs in the two treatment groups were similar. No signal of concern could be detected in the nature or incidence of the SAEs; they were in line with the expected morbidity for an elderly population with AD. The majority of the SAEs in both treatment groups were considered *not related* to study product by the investigator.

Study 99819 Interim Safety Population
As of 31 December 2003, 21 (8%) patients in the *Study 99819 interim safety population* had at least one SAE (including deaths). The most common SAE was accidental injury (4 patients (1.5%)). In the *one-year exposure safety population* from Studies 99679 and 99819, 9 (5.7%) of the 159 patients had at least one SAE. Except for agitation (2 patients), no SAEs in this population were reported by more than one patient. In both interim populations, the majority of the SAEs were considered *not related* to study product by the investigator. As of 15 May 2004 (the cut-off date for the most recent PSUR), a further 21 SAEs had been reported in Study 99819. Overall, the nature and incidence of these SAEs were similar to those reported in the interim analysis of the study and in the completed, double blind, placebo-controlled studies in mild to moderate AD.

Study MD-11
As of 31 March 2004, 78 of the 314 patients in ongoing Study MD-11 had SAEs. Overall, the nature and incidence of these SAEs were similar to those reported in the completed, double-blind, placebo-controlled studies in mild to moderate AD.

Withdrawals due to adverse events

Overall Safety Population
The incidence of withdrawals due to adverse events was 10% in both treatment groups, 175 patients in the memantine group and 159 patients in the placebo group. Not unexpectedly, given the population and the overall adverse event profile, *psychiatric disorders* and *central and peripheral nervous system disorders* were the system organ classes that had the highest overall incidences of adverse events that led to withdrawal in the memantine group.

Study 99819 Interim Safety Population
As of 31 December 2003, only few patients (20 patients (7%)) had withdrawn due to adverse events and the overall rate of withdrawal as well as the rate of withdrawal due to adverse events for patients who had been treated with placebo in the lead-in study (PBO-MEM group) was similar to that for patients who had been treated with memantine in the lead-in study (MEM-MEM group). Also in this population, central and peripheral nervous system disorders and psychiatric disorders were the system organ classes that had the highest overall incidences of adverse events that led to withdrawal. No clear difference in the time to withdrawal due to adverse events between the two treatment sequence groups was seen. No single adverse event led to the withdrawal of more than 2 patients. In the PBO-MEM group, dizziness, headache, and nausea each led to the withdrawal of 2 patients; none of the patients in

the MEM-MEM group withdrew due to these adverse events. Vertigo, agitation, and rash each resulted in the withdrawal of one patient in each treatment sequence group.

Withdrawal Reactions and Abuse Potential

There are no data that indicate that discontinuation of memantine treatment is associated with withdrawal symptoms; however, this issue has not been systematically evaluated. No cases of memantine abuse have been reported.

Over dosage

In the studies of memantine in the treatment of mild to moderate AD, there was one overdose. A 73 year old woman in Study 99819 was hospitalised with confusion and drowsiness following an overdose of carbamazepine (blood level 17.4mg/L (normal therapeutic range 5-10mg/L)) and memantine (100mg). The patient recovered. Overall, the experience with over dosage is limited.

Psychiatric symptoms

NMDA receptor hypofunction has been associated with psychiatric symptoms, and these adverse events (such as hallucinations) deserve special attention. Hallucinations may be caused by memantine in the moderately severe and severe AD population, but not in the less severely affected population. The MAH was requested to specify the severity of AD patients who reported hallucinations and provide a summary of reports from post marketing surveillance.

Clinical Trial Data

In the pooled population of patients with mild to moderate AD from Studies MD-10, MD-12 and 99679 the incidence of adverse event reporting for hallucination was lower in the memantine group (6 patients; 0.8%) than in the placebo group (15 patients; 2.6%). In the Current SPC population of patients with moderately severe to severe dementia the incidence of hallucination was higher in the memantine group (12 patients; 4.1%) than in the placebo group (5 patients; 1.7%). In the overall safety population, which comprises all the adverse event data from both these populations, the overall incidence of hallucination was 1.9% (34 patients) in the memantine group and 2.2% (35 patients) in the placebo group. The incidence of other psychotic-like TEAEs, including delusions, delirium, manic reaction, psychosis, paranoid reaction and paroniria was higher in the placebo group than in the memantine group. Only personality disorder (12 patients, 0.7% on memantine *versus* 5 patients, 0.3% on placebo) and depersonalisation (2 patients, 0.1% on memantine *versus* 0 on placebo) were more frequently reported in the memantine group than in the placebo group. However, the overall frequencies are very low.

Post-marketing Data

From 5-Dec-2001 to 31-Dec-2004 a total of 40 spontaneous reports of hallucinations were received. Of these reports, 17 were serious and 23 were non-serious. The daily dose of memantine for the reported cases ranged from 5 to 20 mg and the treatment duration until onset of symptoms varied greatly.

Of the 17 patients who had hallucination reported as a serious adverse drug reaction, 7 had a history of hallucinations and/or delusions; 1 patient had developed these symptoms during previous memantine treatment, 5 received other drugs or were suffering from other diseases that may have contributed to the occurrence of the event, 1 had a thrombotic stroke and the thrombus was surgically removed coinciding with discontinuation of memantine and 4 had no confounding factors identified

The outcome of the 17 cases of hallucinations reported as a serious ADR was: 2 died, 1 recovered although memantine was continued, 6 recovered after memantine had been stopped or reduced; 1 showed the same symptoms again after re-challenge; in 1, hallucinations worsened when ibuprofen was added to therapy, and improved again after ibuprofen was stopped, but before discontinuation of memantine treatment; in the 1 patient with thrombotic stroke, all symptoms resolved after surgery (memantine was stopped because of the surgery); 1 was recovering after discontinuation of memantine; 1 recovered after discontinuation of memantine and 4 were of unknown outcome

Summary

In the mild to moderate AD studies, the incidence of hallucinations is lower in patients on memantine (0.8%) than in patients on placebo (2.6%). The incidence of hallucinations as an adverse event in the *overall safety population* was also lower with memantine (1.9%) than with placebo (2.2%). Furthermore, the spontaneous reporting of hallucinations in post-marketing monitoring is low. However, it cannot be excluded that memantine may cause or aggravate hallucinations in patients with severe Alzheimer's disease. Patients in these stages of the disease may also be more susceptible to pharmacodynamic effects of drugs. Therefore, hallucination was retained in the SPC as an uncommon ADR for patients with severe AD, under *4.8 Undesirable Effects*.

2.4 SAFETY EVALUATION

The safety profile observed in the moderate to severe AD population did not differ substantially from that seen in the current SPC population. TEAEs with incidence on memantine of 1% or more above the placebo incidence were considered to be Adverse Drug Reactions and are included in the product information of memantine. The pooled placebo-controlled data suggest that headache, somnolence, constipation and dizziness are common adverse drug reactions to memantine. Fatigue, confusion, hallucinations in severe AD patients, vomiting and gait abnormal are listed as uncommon ADRs and seizures as a very rare ADR. Somnolence and constipation are new common adverse reactions as compared to the current SPC.

The CHMP agreed with the proposed amendments to the current SPC including data from the mild to moderate AD population as well as those data from the post-marketing experience.

2.5 CHANGES TO THE PRODUCT INFORMATION

Section 4.1 Therapeutic indications

Treatment of patients with moderate to severe Alzheimer's disease.

Section 4.8 Undesirable effects

In clinical trials in mild to severe dementia, involving 1784 patients treated with memantine and 1595 patients treated with placebo, the overall incidence rate of adverse events with memantine did not differ from those with placebo; the adverse events were usually mild to moderate in severity. The most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were dizziness (6.3% vs 5.6%, respectively), headache (5.2% vs 3.9%), constipation (4.6% vs 2.6%) and somnolence (3.4% vs 2.2%).
The following Adverse Drug Reactions listed in the Table below have been accumulated in clinical studies with memantine and since its introduction in the market.

Body as a whole – general disorders	Common Uncommon	Headache Fatigue
Psychiatric disorders	Common Uncommon Uncommon	Somnolence Confusion Hallucination*
Gastro-intestinal system disorders	Common Uncommon	Constipation Vomiting
Central & Peripheral nervous system Disorders	Common Uncommon Very rare	Dizziness Gait abnormal Seizures

Adverse reactions are ranked according to system organ class, using the following convention: very common (> 1/10), common (>1/100 and < 1/10), uncommon (> 1/1,000 and < 1/100), rare (>1/10,000 and < 1/1,000), very rare (< 1/10,000) including isolated reports.

*Hallucination has mainly been observed in patients with severe Alzheimer´s disease.

Section 4.9 Overdose

There have been very few cases of overdose.
In the case of overdosage (a suicide attempt) for which the highest memantine dose has been reported, the patient survived the oral intake of up to 400 mg memantine with effects on the central nervous system (that is, restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness) that resolved without permanent sequelae.

Section 5.1 Pharmacodynamic properties

Clinical studies
A pivotal monotherapy study in a population of patients suffering from moderate to severe Alzheimer's disease (MMSE total scores at baseline of 3 - 14) included a total of 252 outpatients. The study showed beneficial effects of memantine treatment in comparison to placebo at 6 months (observed cases analysis for CIBIC-plus: p=0.025; ADCS-ADLsev: p=0.003; SIB: p=0.002).

A pivotal monotherapy study of memantine in the treatment of mild to moderate Alzheimer's disease (MMSE total scores at baseline of 10 to 22) included 403 patients. Memantine-treated patients showed a statistically significantly better effect than placebo-treated patients on the primary endpoints: ADAS-cog (p=0.003) and CIBIC-plus (p=0.004) at Week 24 (LOCF). In another monotherapy study in mild to moderate Alzheimer's disease a total of 470 patients (MMSE total scores at baseline of 11-23) were randomised. In the prospectively defined primary analysis statistical significance was not reached at the primary efficacy endpoint at week 24.

A meta-analysis of patients with moderate to severe Alzheimer's disease (MMSE total scores < 20) from the six phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies with patients on a stable dose of acetylcholinesterase inhibitors) showed that there was a statistically significant effect in favour of memantine treatment for the cognitive, global, and functional domains. When patients were identified with concurrent worsening in all three domains, results showed a statistically significant effect of memantine in preventing worsening, as twice as many placebo-treated patients as memantine-treated patients showed worsening in all three domains (21% vs. 11%, p<0.0001).

The package leaflet has been amended accordingly. In addition, minor linguistic changes were introduced in Annex I and IIIB. The CHMP agreed with all the changes proposed by the MAH.