IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Memantine in Alzheimer's disease[1]

Executive Summary

[1] Translation of the executive summary of the final report "Memantin bei Alzheimer Demenz" (Version 1.0; Status: 08.07.2009). Please note that this translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive Summary

Background

The Institute for Quality and Efficiency in Health Care (IQWiG) was commissioned by the Federal Joint Committee (G-BA) to assess the benefit of memantine in the treatment of Alzheimer's disease.

Research question

The aims of the present investigation were:

- to assess the benefit of long-term treatment with memantine for Alzheimer's disease compared to placebo with regard to patient-relevant outcomes
- to assess the benefit of long-term treatment with memantine for Alzheimer's disease compared to treatment with a different drug or non-drug therapy option with regard to patient-relevant outcomes.

Methods

In August 2007 interested parties were invited to submit written comments on the report plan of the present benefit assessment and on Amendments 1 and 2 to the report plan (hearing). As there were no unclear aspects arising from the written comments on the report plan, a scientific debate was not required. The final report plan was subsequently prepared, taking account of all comments received, and published in February 2008.

The assessment was carried out based on randomized controlled trials (RCTs) and, if necessary, on subgroup analyses of participants receiving approval-compliant treatment. The trials were to have a duration of at least 16 weeks and investigate memantine in patients with moderate to severe Alzheimer's disease. Accordingly, the bibliographic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (Clinical Trials) were systematically searched (in each case up to October 2008). In addition, literature indexes of relevant secondary publications, study and study results registries and publicly accessible drug approval documents were searched (last search of study registries: January 2009). The manufacturers of memantine were also asked to provide information on relevant published or unpublished studies.

The literature screening was carried out by 2 reviewers independently of each other. After assessing the study quality, the results of the individual studies classified according to outcomes were compared and described. These were subdivided into patient-relevant, family-relevant and supplementary outcomes.

IQWiG's preliminary benefit assessment, the preliminary report, was published on the Internet in August 2008 and interested parties were invited to submit written comments. Unclear aspects arising from the written comments were discussed in a scientific oral debate in January 2009. The final report was prepared after the oral debate.

Results

A literature search was carried out in the relevant bibliographic databases, secondary publications were screened, study registries and publicly accessible approval documents were searched, and manufacturers and authors contacted, resulting in 12 relevant studies being identified.

Out of the 7 studies included, 5 compared memantine monotherapy with placebo (10116, 99679, MEM-MD-01, MEM-MD-10, MRZ-9605); MEM-MD-02 and MEM-MD-12 investigated memantine compared to placebo as an add-on to a cholinesterase inhibitor. None of the included studies investigated memantine compared to another drug or non-drug treatment. In 4 of these studies, the use of memantine was not fully approval-compliant, because memantine and/or the cholinesterase inhibitor concomitant medication were used for a non-approved AD (Alzheimer's disease) severity grade. The manufacturers provided relevant subgroup analyses for the assessment within the scope of the approval. None of the included studies had a follow-up period of more than 28 weeks.

Five studies could not be included in the assessment as there were not sufficient data for the assessment. For 2 of these studies, there was no response from the authors for subgroup analyses of participants receiving approval-compliant treatment (Hu 2006) or for a publication of the complete results (MEDUSA). At the time of preparing the report, there was no analysis available for the third study (Alzheimer COMBI). In the case of 2 manufacturer-sponsored studies, the study report was not made available by the manufacturer despite being asked to do so (MEM-MD-22 and IE-2101). Due to their size, these 2 manufacturer-sponsored studies in particular have the potential to alter the result of the assessment, although this probably amounts at most to removing the significance in the outcomes "activities of daily living" and "cognitive function".

The following studies displayed minor flaws: 99679, MEM-MD-01, MEM-MD-02, MEM-MD-10, MEM-MD-12 and MRZ-9605. Study 10116 displayed major flaws, as it was established that a systematic error had evidently occurred in the data documentation in one study centre. The results of a post-hoc ITT-LOCF[2] analysis (which would have been desirable) excluding the data of the afore-mentioned centre were nevertheless not presented in the study report.

Table 1 summarizes the results of the benefit assessment for the individual outcomes.

[2] intention to treat-last observation carried forward

Table 1: Summary of the results for the outcomes

Outcome	Memantine vs. placebo (as mono or ChE-I add-on therapy)	Memantine vs. other drug or non-drug therapy options
Patient-relevant outcomes		
Impairment of activities of daily living	⇔	no data
Cognitive function	⇔	no data
Health-related quality of life	no data	no data
Concomitant psychopathological symptoms	⇔	no data
Necessity of inpatient care (institutionalization)	data collected, not available or mostly not analysable	no data
Mortality	(⇔)	no data
Adverse drug effects	⇔	no data
Family caregiver-relevant outcomes		
Quality of life of family caregivers	⇔	no data
Resources required by one or more caregivers or institutions	data collected, mostly not analysable	no data
Supplementary information		
Clinical stage of disease according to clinical impression	⇔	no data
ChEI: cholinesterase inhibitor ↑↑, ↓↓ = proof of favourable/unfavourable effect ↑, ↓ = indication of favourable/unfavourable effect ⇔ = no proof of difference ( ) = few data available		

In the meta-analyses on the individual outcomes, the results of the mono and add-on therapy studies, which investigated memantine as an add-on to a cholinesterase inhibitor, were shown separately within the total meta-analysis. As a result, a separate conclusion on the mono and the add-on therapy was not necessary.

Statistically significant effects in favour of memantine were found in the meta-analysis for both the **impairment in activities of daily living** and **cognitive function** outcomes. The standardized effect sizes in favour of memantine were 0.14 (95 % CI [0.05; 0.23]) and 0.20 (95 % CI [0.07; 0.33]) respectively. As no data for estimating the relevance of these effects or the observed effect strengths could be identified for the scales used, a standardized effect size of 0.2 was used as a threshold value for assessment. In both cases the lower limit of the confidence interval lay below this threshold. The relevance of this effect could therefore not be estimated with certainty. Thus there is no proof of benefit of memantine for the outcomes "activities of daily living" and "cognitive function". The certainty of the conclusion is further reduced because several studies could not be included in the assessment, in particular 2 larger, manufacturer-sponsored studies (IE2101 and MEM-MD-22) with 580 patients, for which insufficient data were provided.

There were no data on the **health-related quality of life** outcome, consequently there is no proof of benefit of memantine for this outcome.

In the meta-analysis there was no statistically significant effect on the basis of the available data for the **concomitant psychopathological symptoms** outcome. This contradicts the findings in a published meta-analysis based on individual patient data (IPD). However, the validity of this analysis is limited for the following reasons:

- patients from the MEM-MD-02 study receiving non-approval-compliant treatment were also included
- the patient collective analysed is larger than the available data indicate
- Study 10116 was not included in the analysis

A relevant analysis based on the available, aggregated data shows high heterogeneity, so that the data from an effects estimator is not meaningful. Irrespective of that, there were doubts as to the relevance of the effect described in the IPD meta-analysis: standardized effect size: 0.10 (95 % CI [0.01; 0.19]). In addition, the IE2101 and MEM-MD-22 studies were excluded, although the publication was produced with the collaboration of one of the manufacturers. Overall, no proof of benefit of memantine could be deduced for the "concomitant psychopathology" outcome from the available data.

There were no analysable data available on the **necessity of inpatient care** (institutionalization). Relevant data were collected in MEM-MD-01, MEM-MD-02, MEM-MD-10, MEM-MD-12 and MRZ-9605, but were neither published nor provided in the form of manufacturer's documents. On the basis of this, it was not possible to identify a proof of benefit of memantine for this outcome.

No proof could be identified of a change in the **mortality** outcome under memantine therapy compared to placebo. However, there was little data available and in particular no studies focussing on this outcome.

The data available on study discontinuations due to adverse events and severe adverse events produced no proof of an increased risk of **adverse drug effects** under memantine therapy compared to placebo.

None of the included studies defined **quality of life of family caregivers** as an outcome. On the basis of the available results from the NPI-D instrument, which depicts a partial aspect, it was not possible to identify an effect of memantine on this outcome.

With reference to the second family caregiver-relevant outcome, **resources required by one or more caregivers or institutions**, there was in fact a statistically significant effect in favour of memantine in MRZ-9605, but the data collected in MEM-MD-01, MEM-MD-02, MEM-MD-10 and MEM-MD-12 were neither published nor provided in the form of manufacturer's documents. On the basis of this, therefore, it was not possible to identify an effect of memantine on this outcome.

The meta-analysis showed a statistically significant effect on the supplementary outcome, **clinical stage of disease according to clinical impression**. The standardized effect size in favour of memantine was 0.18 (95 % CI [0.05; 0.30]). No data for estimating the relevance of this effect or the observed effect strengths on a group level could be identified for this scale. There were no responder analyses available for the defined relevance limit on an individual level. A standardized effect size of 0.2 was therefore used as a threshold value for the assessment. As the lower limit of the confidence level lay below this threshold, the relevance of this effect could not be estimated with certainty. From the available data, therefore, it was not possible to deduce a proof of a relevant effect from memantine for this outcome. The certainty of the conclusion is further reduced as several studies could not be included in the assessment, in particular 2 larger, manufacturer-sponsored studies (IE2101 and MEM-MD-22) with 580 patients, for which insufficient data were provided.

Due to various factors, which differentiated this study from the others, it was unclear whether Study 10116 could be justifiably included in the meta-analysis. Consequently, sensitivity analyses were carried out in each case without this study in order to test the robustness of the result. This procedure complied with the designated sensitivity analyses concerning the minimum study duration of 6 months [1] recommended by the EMEA[3] and concerning the certainty of results based on the biometric quality. No differing result was recorded in any of these sensitivity analyses.

[3] European Medicines Agency

In order to check whether a relationship exists between the proportion of patients who were not fully followed up and the results, sensitivity analyses were carried out in which the effect estimators of studies with discontinuation rates below 20 % were compared with those with discontinuation rates above 20 %. These analyses did not lead to any change in the assessment.

There were no indications of subgroup-specific effects from memantine therapy either from the pre-planned **subgroup analyses** or from the analyses provided on request by the manufacturers on the impact of the degree of disease severity.

Conclusions

There is no proof of benefit from memantine therapy for patients with Alzheimer's disease. This applies equally to patients with moderate and severe Alzheimer's disease. There is also no proof of benefit for treatment either as a monotherapy or in combination with other anti-dementia drugs.

In the outcomes "activities of daily living" and "cognitive function", effects from memantine therapy are visible. However, due to the low occurrence of these effects, their relevance is debatable, so that a benefit from memantine treatment cannot be deduced.

The data on adverse events from memantine therapy produced no proof of an increase in harm potential compared to placebo.

All conclusions refer only to a treatment period of up to 6 months. Long-term studies on memantine are lacking.

Studies on a direct comparison of memantine with other drug and non-drug treatment options are not available.

Keywords: memantine, Alzheimer's disease, dementia, benefit assessment, Health Technology Assessment, systematic review

The full report (in German) is available on www.iqwig.de/index.404.html.