MEMANTINE FOR THE TREATMENT OF ALZHEIMER’S DISEASE

Lundbeck Response to the Appraisal Consultation Document

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Introduction

Lundbeck is pleased to submit its response to the NICE Appraisal Consultation Document (ACD) on the multiple technology appraisal (MTA) of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (AD) (review of NICE technology appraisal guidance 111).

Lundbeck would like to express their appreciation to the NICE Appraisal Committee and the Peninsula Technology Assessment Group (PenTAG) for their comprehensive review of the data for memantine. In particular, Lundbeck would like to thank the Committee for the consideration of their feedback on the technology assessment report (TAR) developed by PenTAG. We believe that the revision of several elements of the PenTAG assessment, particularly in relation to the economic model, in response to the comments from Lundbeck and other stakeholders, has ensured that the evaluation of the evidence for memantine is now improved in terms of robustness and validity.

Lundbeck feel that the NICE MTA for AD treatments has been a transparent process that has ensured that all AD patients in England and Wales, including those in the most advanced and severe stages of the disease, will now get access to clinically effective medications that represent the most efficient use of NHS resources.

The Lundbeck response to the NICE ACD has three main components. Firstly, while Lundbeck recognise that much of their feedback on the TAR was considered and implemented we feel it is important to highlight several aspects that relate to the differences in approach between the Lundbeck review of the data and the PenTAG approach, which gave rise to conflicting conclusions on the efficacy of memantine as an adjunct treatment to acetylcholinesterase inhibitors (AChEIs). Secondly, feedback is also provided on the approach to the use of individual patient data, with the aim of starting a dialogue that will facilitate the use of such data in future appraisals. Finally, comments and suggested amendments on specific aspects of the ACD are provided.
1 Differences between the Lundbeck and PenTAG Approach

This section will consider the differences in approach to both the clinical evaluation of memantine and to the economic evaluation.

1.1 Clinical Evaluation

There are several differences between the Lundbeck and PenTAG conclusions on the efficacy of memantine in the treatment of AD. These conflicting results can be explained by an examination of the approach taken by Lundbeck and PenTAG to the evaluation of the clinical data. Lundbeck believe that it would be useful to elaborate on these differences in the ACD in order to improve the clarity for readers. This is described in more detail below.

The main clinical evidence package for memantine consists of 6 six-month randomised placebo-controlled trials:

- Three in patients with moderately severe to severe AD, including two with memantine monotherapy (FRX-MD-01\textsuperscript{1}, MRZ-9605\textsuperscript{2}) and one with memantine as an adjunct to donepezil (FRX-MD-02\textsuperscript{3})
- Three in patients with mild to moderate AD including two with memantine monotherapy (Lu-99679\textsuperscript{4}, FRX-MD-10\textsuperscript{5}) and one with memantine as an adjunct to AChEIs (FRX-MD-12\textsuperscript{6})

It is important to first highlight the major difference in the way the clinical data for memantine in the treatment of AD was considered.

The Lundbeck synthesis of the evidence pooled data from all six trials but, in line with the memantine licence, excluded mild patients from trials that included mild-moderate AD. This meta-analysis of the data has been published in a peer reviewed journal.\textsuperscript{7} The mixed patient population in the Lundbeck analysis was composed of:

- Moderate AD patients withdrawn from AChEIs;
- Moderate patients contraindicated for AChEIs;
- Moderate patients requiring adjunct treatment while on stable dose with AChEIs; and
- Patients with severe AD.

The key conclusions of this published meta-analysis, as highlighted in the Lundbeck submission, were:

“A statistically significant treatment effect in favour of memantine was found with respect to all four key efficacy domains. Memantine was found to be effective in attenuating deterioration of cognition, function, behaviour and global status (Table 3.1) and no evidence of heterogeneity was found for the data analysed. This analysis was published by Winblad et al., 2007”
An investigation of potential differences in the memantine efficacy according to the included patients' profiles (severity, presence of background AChEI treatment and history of past AChEI treatment) revealed no heterogeneity in the memantine efficacy across the different groups and the pooling of data across these populations is therefore appropriate. In particular, the efficacy of memantine versus placebo as adjunct treatment or monotherapy, and the interaction between treatment effect and presence or absence of background treatment was assessed and found to be non significant. This is clearly stated in the appendix of the Lundbeck submission for memantine:

“Memantine was significantly superior to placebo on most outcomes, both as adjunct therapy and monotherapy. Other outcomes, namely disability in adjunct (p=0.0551 in OC and p=0.0600 in LOCF) and global health state in adjunct for the LOCF analysis (p=0.0666), were close to significance level, despite lower sample size compared with base case analyses. The interaction between treatment effect and presence of background treatment was not significant.”

In contrast to the approach taken by Lundbeck, PenTAG considered the clinical efficacy of memantine in two separate groups:

- A monotherapy analysis including only the two trials in moderately severe to severe AD (FRX-MD-01, MRZ-9605). This did not include the monotherapy trials in mild-moderate patients (Lu-99679, FRX-MD-10) as data in the moderate population only were not included in the primary publications of these trials. However, it should be noted that the data in the moderate patient sub group was available in published meta-analyses.7
- An adjunct analysis including the clinical trial in moderately severe to severe patients (FRX-MD-02) and in mild moderate patients (FRX-MD-12). It is important to note that in their analysis PenTAG included all patients from trial FRX-MD-12 despite some patients having mild AD and therefore being outside the current licensed indication for memantine.

The reasons for PenTAG choosing to synthesise the data as described above are unclear. It would have been possible for PenTAG to exclude the mild patients from trial FRX-MD-12 and there appears to be no justification for why this approach was adopted.

In the ACD the following PenTAG conclusions on the efficacy of memantine as an adjunct treatment to AChEIs are described:

NICE statement, ACD 4.1.40 p26: “The Assessment Group found one new trial that compared memantine plus a stable dose AChE inhibitor with an AChE inhibitor plus placebo. This trial did not show any benefit from combining memantine with an AChE inhibitor on cognitive, functional, behavioural or global outcomes. A trial that compared memantine plus donepezil with donepezil plus placebo was included in NICE technology appraisal guidance 111. Pooling the new trial with the previous trial of memantine in combination with an AChE inhibitor did not show any additional benefit from combination therapy.”

NICE statement, ACD 4.3.14 p52: "The Committee noted evidence that showed no statistically significant benefit for combination treatment with memantine and AChE inhibitors for cognitive, functional, behavioural or global outcomes.“
The discrepancy between the PenTAG and Lundbeck conclusions on the efficacy of memantine as an adjunct treatment to AChEIs can be explained by the different approaches. While PenTAG included all patients from study FRX-MD-12 in their meta-analysis (including mild patients who fall outside memantine indication), Lundbeck included only moderate patients from this study. In the ACD the lack of significant benefit in study FRX-MD-12 is highlighted although no reference is made to the significant efficacy that was reported in FRX-MD-02 across all the domains; cognition, functional disability, behaviour and global. This omission is particularly important as study FRX-MD-02 is the only trial for adjunctive use of memantine that includes exclusively patients within the licensed indication for memantine.

The differences between the included studies are described in the ACD, but they are stated only very briefly and this does not provide sufficient information:

**NICE statement, ACD 4.1.43 p27:** "The Assessment Group concluded that the evidence in the three manufacturer’s submissions was broadly consistent with its own, but highlighted that there were differences between the studies included by the manufacturers and its own review."

In order to enhance the transparency of the recommendations for readers, it is proposed that the results from the Lundbeck pooled analysis of all patients, in line with the memantine licence, should be described in more detail, and the differences between this analysis and the PenTAG approach in regards to the adjunct memantine analysis is highlighted.

Lundbeck proposes that the following statements should be included in the ACD:

- Study FRX-MD-02 conducted in moderately severe to severe AD (thereby completely within the memantine indication) concluded that there was a significant benefit from combination treatment with memantine plus donepezil compared to donepezil alone on all four domains of AD symptoms: cognition, functional disability, behaviour and global.
- Although study FRX-MD-12 showed no significant benefit with memantine in the total population of mild to moderate patients the differences in the baseline severity of the patients from FRX-MD-02 and FRX-MD-12 are a possible reason for the differences in clinical outcomes.
- When the data was pooled and the mild patients, who are not within the memantine indication, were excluded a significant benefit of memantine as an adjunct to AChEIs was reported.
1.2 Economic Evaluation

It is important to note that the Lundbeck and PenTAG conclusions on the cost-effectiveness of memantine were consistent overall despite some differences in modelling approach.

In terms of the cost-effectiveness evaluation, the difference in the approaches taken by Lundbeck and PenTAG to the clinical evaluation also explains the variation in the choice of data sources for the economic model. With the Lundbeck economic evaluation the LASER-AD cohort was used to develop the cost-effectiveness model. This observational study is most representative of current management of AD patients in the UK, and within this study patients could be treated with or without AChEIs. In contrast the PenTAG economic model utilised an observational cohort (the Wolstenholme study) in which patients received no AD treatments.
2 Access to Individual Patient Data

As stated during the Appraisal Committee meeting held on the 25th of August, Lundbeck is not opposed to the submission of individual patient data (IPD) from clinical trials to NICE if this is deemed necessary in order to improve the evaluation process. It should be noted that PenTAG did not request any IPD from Lundbeck to assist them in their evaluation of the efficacy of memantine.

Lundbeck feel there are several important practical issues that should be highlighted in regard to the submission of IPD:

- Memantine is licensed by Lundbeck but also by partner companies and therefore authorisation from these partners would be required before Lundbeck could release data to NICE or to PenTAG;
- All partners contributed to the clinical trial development of memantine and different standard database formats were used across the memantine trials. The PenTAG analysts would therefore require training on all utilised database formats;
- All analyses of IPD from clinical trials performed by PenTAG should be assessed by the manufacturers, who are familiar with the datasets, to ensure quality of the programming and of the analyses.

The practical issues highlighted above are relevant not only for the appraisal of memantine but also for many other therapies being developed by Lundbeck. Due to the current size of Lundbeck, the vast majority of products in development are being co-developed with partner companies and therefore the first two issues described above are of particular importance.

In order to ensure that any future technology appraisals are conducted in the most robust and transparent way possible, Lundbeck would be very pleased to discuss the development of a process for the sharing of IPD with NICE and the analysis of this data by the independent academic group.
3 Specific Comments

The following section offers specific comments on the ACD with the proposed amendments by Lundbeck.

3.1 Data on Observational Studies

The observational data for donepezil is comprehensively included in the ACD as supporting the clinical benefit of this therapy, as follows:

NICE statement, ACD 4.1.11 p16: “The manufacturer of donepezil included prospective longitudinal and observational studies to support the view that cognitive benefits from donepezil are maintained for up to 3 years. The manufacturer also presented evidence from randomised and nonrandomised controlled trials to demonstrate that benefit was lost when treatment was stopped, the benefits of continuing treatment despite initial decline or stabilisation of MMSE, and the impact of improvement of neuropsychiatric symptoms on caregiver stress and burden.”

For memantine there are a number of observational studies that provide data to support the controlled trial data, and in the ACD the following is included for memantine:

NICE statement, ACD 4.1.32 p23: “Evidence from observational studies was also presented.”

Although NICE mention the observational studies submitted by Lundbeck for memantine a summary of the findings from this data was not integrated in the ACD. In order to ensure the consistent presentation of observational data across the AD treatments considered in the technology appraisal Lundbeck suggest the inclusion of the following paragraph within the ACD:

“The manufacturer of memantine included prospective longitudinal and observational studies which support the view that the cognitive and functional benefits of memantine are maintained for years (Atri et al., 2008), that memantine delays time to institutionalisation (Lopez et al., 2009), that memantine initiation reduces the trend in increasing antipsychotic drug use among AD patients (Vidal et al., 2008), that memantine treatment reduces the need for antipsychotic medication (Martinez et al., 2008a and 2008b) and that memantine discontinuation is associated with an increased utilisation of antipsychotics compared to continuous memantine treatment (Fillit et al., 2008a and 2008b).”

3.2 Safety of Memantine

NICE statement, ACD 4.3.15 p53: “The Committee considered the evidence of adverse effects associated with memantine and noted that some patients experience agitation that resolves when the drug is stopped.”

In the TAR, this statement was based on one study only. Lundbeck believes that this conclusion is unfair and does not reflect the full evidence available for memantine, which actually shows fewer agitation adverse events in memantine treated patients compared to placebo treated patients. This reduction of agitation adverse events is consistent with the
efficacy of memantine on the symptom of agitation that is acknowledged by NICE in the current ACD. The relevant extract from the Lundbeck response to the TAR is provided below:

"In the TAR data on the safety for memantine as a monotherapy is reported based on one study only MEM-MD-12 (in which patients are treated with stable dose of AChEIs) and reports that “the main AEs in the memantine group were agitation and hypertension” (section 4.6.4.3.6; page 153). It should be noted that the incidence of agitation was lower in memantine treated patients than placebo treated patients. In the case of safety it is more appropriate to synthesise data across multiple trials. A meta-analysis on the tolerability and safety data from clinical trials published in 200814 would be a more appropriate source of safety data. Other reviews of safety data from all memantine clinical trials are also available. This analysis reports that the most common adverse events with memantine are agitation and falls and both have numerically lower incidence than placebo.”

We would therefore propose that the wording in the ACD should be rewritten to read as follows:

"The Committee considered the evidence of adverse effects associated with memantine. The main AEs in the memantine group were agitation and hypertension, but the incidence of agitation was lower in memantine-treated patients than placebo treated patients.”

### 3.3 Inclusion of Additional Details on the Meta-Analysis

As described previously, the approach to the evaluation of the clinical data by Lundbeck and PenTAG differed, with the differences in the trials included in the meta-analyses conducted by both groups. The meta-analysis reported by Lundbeck is included in the ACD as described below:

NICE statement, ACD 4.1.33 p24: “Studies included in the manufacturer’s meta-analysis for memantine reported a statistically significant benefit in ADAS-cog or SIB compared with placebo at the end of study or at 24 weeks.”

NICE statement, ACD 4.1.34 p24: “The manufacturer’s meta-analysis for memantine in moderate to severe disease showed a statistically significant difference compared with placebo on the ADCS-ADL19 and ADCS-ADL23.”

NICE statement, ACD 4.1.35 p24: “The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant (p = 0.03) benefit in terms of NPI and NPI-Nursing Home version.”

NICE statement, ACD 4.1.36 p25: “The standard mean difference in the manufacturer’s meta-analysis for memantine in moderate to severe disease for global outcomes (CIBIC-plus) compared with placebo was statistically significant.”

In the ACD the conclusions from the PenTAG analysis are supported by the accompanying data, as shown in the example below:

NICE statement, ACD 4.1.33 p23-24: “When data from this trial were added to those of NICE technology appraisal guidance 111, a statistically significant benefit was reported at 12
weeks, but this was not maintained at 24-48 weeks (mean changes from baseline versus placebo of 4.147 \([p = 0.025]\) and 3.254 \([p = 0.245]\) at 12 and 24/28 Weeks using SIB score)."

We suggest that adding figures from the Lundbeck analysis in the text will increase the transparency for the reader. The following suggestions are recommended:

**NICE statement, ACD 4.1.33 p24** “Studies included in the manufacturer’s meta-analysis for memantine reported a statistically significant benefit in ADAS-cog or SIB compared with placebo at the end of study or at 24 weeks \((SMD = -0.26, p < 0.0001)\).”

**NICE statement, ACD 4.1.34 p24:** “The manufacturer’s meta-analysis for memantine in moderate to severe disease showed a statistically significant difference compared with placebo on the ADCS-ADL19 and ADCS-ADL23 \((SMD = -0.18, p = 0.007)\).”

**NICE statement, ACD 4.1.35 p24:** “The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant \((SMD = -0.12, p = 0.03)\) benefit in terms of NPI and NPI-Nursing Home version.”

**NICE statement, ACD 4.1.36 p25:** “The standard mean difference in the manufacturer’s meta-analysis for memantine in moderate to severe disease for global outcomes (CIBIC-plus) compared with placebo was statistically significant \((SMD = -0.22, p < 0.0001)\).”

### 3.4 Miscellaneous Comments and Suggested Amendments

The following text amendments are suggested to correct inaccuracies and provide additional clarification for the reader.

1. **NICE statement, ACD 4.1.24 p20:** “These used the Progressive Deterioration Scale (PDS) and ADCL-ADL as outcome measures.”

In this sentence, “ADCL-ADL” should be changed to “ADCS-ADL”.

2. **NICE statement, ACD 4.2.25 p40:** “The manufacturer submitted a Markov cohort model of the cost effectiveness of memantine compared with best supportive care over a 5-year time horizon in people with moderate to severe Alzheimer’s disease and a subgroup of people with aggression, agitation and/or psychotic symptoms at baseline based on the NPI scale \((\geq 3)\).”

To improve the transparency of the subgroup definition, the bold text should be changed to “based on the NPI scale (at least one domain among agitation/aggression, delusion and hallucination with a score \(\geq 3\))”

3. **NICE statement, ACD 4.2.28 p41:** “The subgroup that was analysed had not previously been accepted by the Appraisal Committee for NICE technology appraisal guidance 111.”
Lundbeck acknowledges that a subgroup analysis in behaviourally disturbed patients was previously submitted to NICE for technology appraisal guidance and was not accepted by the Appraisal Committee. However, the subgroup analysis presented here represents patients with APS (agitation/aggression and/or psychosis), and is different to that previously submitted. This APS subgroup is defined based on the grounds of clinical expertise (please see appendix B of the Lundbeck submission “Consensus Statement on APS Sub-group Definition”).

4. NICE statement, ACD 4.2.28 p42: "In addition, because the trials used observed cases with last observation carried forward in the analysis instead of an intention-to-treat analysis, the Assessment Group was concerned that the clinical-effectiveness estimates may have been biased.”

As stated in the Lundbeck response to the TAR: "studies use the same criteria to define the population analysed (All randomised patients who took at least one dose of investigational medicinal product (memantine or placebo) and had at least one valid post-baseline assessment on primary endpoint)". Therefore, all analyses have been performed on intent-to-treat population using the observed cases approach, with a last observation carried forward analysis also included to confirm the results. Lundbeck request that the statement is removed.

5. NICE statement, ACD 4.2.33 p44: "The manufacturer’s model also assumed a higher cost of, and a shorter time in, pre-institutional care with treatment (1.73 years in the manufacturer’s model compared with 1.5 years in the Assessment Group’s model)."

This conclusion seems erroneous as a longer time in the pre-FTC state is observed in the Lundbeck model (1.73 years) compared to the time in pre-institutionalisation in PenTAG model (1.5 years). "Shorter time" should be changed to "longer time".

6. NICE statement, ACD 4.3.13 p52: "This evidence reported a statistically significant benefit of memantine for cognitive outcomes and neuropsychiatric inventory score on agitation, aggression and/or psychotic symptoms in this subgroup."

NICE statement, ACD 4.3.35 p63: "The Committee also heard from clinical specialists and the manufacturer that memantine appears to have cognitive and behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms, which are more common in people with severe Alzheimer’s disease.”

In order to more accurately reflect all the findings from the analyses of memantine efficacy in the subgroup, these paragraphs should be changed as follows:

NICE statement, ACD 4.3.13 p52: "This evidence reported a statistically significant benefit of memantine for cognitive, **functional and global** outcomes and neuropsychiatric inventory score on agitation, aggression and/or psychotic symptoms in this subgroup.”
NICE statement, ACD 4.3.35 p63: "The Committee also heard from clinical specialists and the manufacturer that memantine appears to have cognitive, functional and global and behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms, which are more common in people with severe Alzheimer's disease."

7. NICE statement, ACD 4.2.28 p42: "There was also a lack of clarity about the categorisation of 'dependence', inclusion of data from patients with mild disease, poor reporting of statistical analyses and lack of validation from an external source."

NICE statement, ACD 4.2.28 p42: "Benefits to carers were not included in the model, and mapping of health-related quality-of-life data to EQ-5D was poorly described."

Lundbeck believes these statements on their economic model are inappropriate and unfairly represent the evidence submitted. All these issues have been addressed in the answer to the TAR submitted by Lundbeck on the 4th August 2010. In their response, Lundbeck acknowledged the lack of validation of the predictive equation against an external source and clarified all other issues.

Lundbeck would like to highlight that detailed information on each of these points were highlighted both in the memantine dossier and in the Lundbeck response to the TAR and to reiterate that all information required to support their response can be provided upon request. Lundbeck would welcome constructive feedback on how to improve the reporting of such analyses, both in the context of this evaluation and also to enable improved reporting in future appraisals.
References


13 Fillit H, Hofbauer RK, Setyawan J, et al., editors. Memantine Discontinuation in Nursing Home Residents With Alzheimer’s Disease is Associated With an Increase in Alzheimer’s Disease Symptoms. 12th Annual Congress of the European Federation of Neurological Societies; 2008; Madrid, Spain.