APPENDIX 1

Acetylcholinesterase Inhibitors (AChEIs):

A. DONEPEZIL (ARICEPT)

A.1. Summary of available data

A.1.1. Reminder of the re-assessment opinion conclusions of 20 June 2007

Data from the Cochrane meta-analysis (2006)\(^1\) have confirmed that treatment with donepezil 5 or 10 mg/day in patients with Alzheimer's disease was more effective than the placebo in terms of evolution of cognitive function and the overall impression of carers (14 clinical studies) after 3 months, 6 months and 1 year of treatment.

It should be noted that, according to the authors of this work, this benefit was established in patients with Alzheimer's disease at a level of severity qualified as mild to severe (outside of scope of current Marketing Authorisation). A benefit in performing everyday activities and associated behavioural issues was also observed. This modest impact is less well documented. The impact on quality of life was not documented. The level of effect attributed to donepezil at doses of 5 or 10 mg/ day was not significant across all assessment criteria, and the clinical relevance of the effects observed was called in to question, given the size of the effect, and the true impact for patients: as an illustration, a difference of 2.8 points on a composite score on the ADAS-Cog scale of 70 points for cognitive function was seen.

The choice of giving a dosage of 10 mg/day of donepezil over that of 5 mg/day may be discussed based on the results observed: overall marginal additional clinical benefit for 10 mg/day (no difference observed between the two doses on the CIBIC plus, CDR-SB or MMSE scales and a difference of 1 point on the ADAS-Cog scale) but with improved tolerance for the 5 mg/day dosage.

It should be noted that more recent studies have not investigated the 5 mg/day dosage. There are no data available which allows the longer-term effect of donepezil to be determined. The authors of the meta-analysis recall the need to investigate the optimum treatment duration and the indicators for stopping treatment due to an absence of benefits (implications for research).

A.1.2. New clinical efficacy data

In the symptomatic treatment of Alzheimer's disease, no new randomised studies comparing donepezil to placebo have been presented by the laboratory.

Summary of PenTAG report (NICE 2011)

The authors state that no new systematic or meta-analysis with good quality methodology, according to PRISMA\(^2\) recommendations, has been found since 2004.

Five new randomised clinical studies versus placebo were taken into consideration.\(^3\)^\(^4\)^\(^5\)^\(^6\)^\(^7\)

Their study plan, the patient characteristics and an assessment of their internal validity are

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presented in this report (see tables 3, 4 and 5). It should be noted that the methodology of these studies was considered as being unsatisfactory, and that none of them lasted for more than six months.

An intention-to-treat analysis was only presented for two of these new studies. The three other studies used an OC (observed case(s)) analysis method to manage missing data, which tended to overestimate the results in favour of donepezil.

New data is available from five studies on cognitive function (table 6) and from one study on the effects on performing daily activities (table 7) and the clinician's global impression of change (table 8). There is no new data available to allow the re-assessment of the level of effect on behavioural issues, quality of life and adverse effects.

The studies considered by NICE in 2004 were taken into account during the re-assessment in 2007 by the Committee.


EFFECTS ON COGNITIVE FUNCTION:

In 2004, six studies demonstrated the superiority of donepezil versus placebo for cognitive issues, evaluated using the ADAS-Cog scale (possible dose-dependent effect for some studies).

The efficacy results from the four studies on cognitive function are described in table 6. An intention-to-treat analysis was only carried out for two of these studies (Mazza et al, 2006 and Winstein et al, 2007).

There are no new data documenting the effects measured for ADAS-cog at 12 and 24 weeks. A new study documented the effects measured for MMSE at 24 weeks.

The meta-analysis showed a statistically significant effect for donepezil compared with placebo, which increases with time on the ADAS-Cog (0 to 70 points) and MMSE scales (0 to 30 points):

- **ADAS-Cog (see figures 7 and 8).**
  - 12 weeks (10 mg/day) WMD = - 1.97 (95% CI: [-3.38; -0.56]), p = 0.006;
  - 24 weeks (10 mg/day) WMD = - 2.90 (95% CI: [-3.61; -2.18]), p < 0.001.

- **MMSE (see figures 9 and 10).**
  - 12 weeks (10 mg/day) WMD = 1.17 (95% CI: [0.88; 1.45]), p <0.001
  - 24 weeks (5 mg/day and 10 mg/day) WMD = 1.21 (95% CI: [0.84; 1.57]), p < 0.001

An pooled analysis of all nine studies including results on the cognitive function at 24-26 weeks showed a favourable effect for donepezil compared with placebo: SMD = 0.40 (95% CI: [0.29; 0.50]), p<0.001 (figure 11; Appendix 6).

IMPACT ON EVERYDAY ACTIVITIES:

In 2004, an assessment of the effects of donepezil was carried out based on the results from eight studies versus placebo. The effect of donepezil was superior to that of placebo, in the improvement or the limitation of the deterioration of performing daily activities, assessed on the ADL scale. This effect was poorly established and no difference, compared with placebo, was highlighted in the studies that took place over longer periods.

In a different study (Peng et al, 2005, table 7), a significant effect at 12 weeks with donepezil (5 mg/day) was highlighted on the ADL scale (according to an analysis that was not ITT-based) compared with placebo: mean score with donepezil = 40.5 (SD 7.6), mean score with placebo = 49.5 (SD 6.3), p <0.01.

At 24 weeks, there was no new data.

The meta-analysis did not allow the size of the effect to be quantified, taking the heterogeneity of the assessment criteria into account.

After 24 weeks of treatment, a pooled analysis of the studies nevertheless found a favourable effect for donepezil (all doses) versus placebo: SMD = 0.30 (95% CI [0.14; 0.45]), p<0.001 (figure 12 and Appendix 6).
EFFECTS ON BEHAVIOURAL ISSUES:

Four clinical studies suggested a possible effect on demeanour and behaviour, measured on the NPI scale. There is no new data in the PenTAG report. It should be noted that a comparative study, not taken into consideration in the PenTAG report, evaluated the efficacy of 10 mg/day of donepezil versus placebo to treat agitation, considered as being clinically significant, in 272 patients diagnosed with Alzheimer's disease. This agitation had not been successfully treated with previous psychosocial treatments. After 12 weeks of treatment, no difference between donepezil and placebo was observed according to the assessment measured using the following scales: Cohen Mansfield Agitation Inventory (primary efficacy endpoint), Neuropsychiatric Inventory, Neuropsychiatric Inventory Caregiver Distress Scale and Clinician's Global Impression of Change.

The meta-analysis of studies already considered, did not show a significant effect for donepezil compared with placebo at 12 and 24 weeks (figures 13 and 14).

EFFECT BASED ON OVERALL ASSESSMENT (CLINICAL GLOBAL IMPRESSION OF CHANGE):

In 2004, seven clinical studies evaluated the effect of donepezil compared with placebo using the CGIC or CIBIC Plus scales: the efficacy of donepezil was not clearly established. The meta-analysis of the studies considered in 2004 showed a significant effect for 10 mg/day of donepezil compared with placebo, according to the CIBIC-Plus scale (figures 15 and 16):

- at 12 weeks: WDM = - 0.38 (95% CI: [-0.49; -0.26]), p <0.001
- at 24 weeks: WDM = - 0.43 (95% CI: [-0.55, -0.31]), p <0.001.

A different study (Peng et al, 2005) highlighted a statistically significant difference between donepezil and placebo using the Clinical Dementia Rating (CDR) scale: mean score with donepezil = 1.2 (SD 0.2), mean score with placebo = 2.0 (SD 0.2), p <0.01 (table 8). The meta-analysis of results with the CDR scale (figures 17 and 18) showed a statistically significant difference between 10 mg/day of donepezil and placebo:

- at 12 weeks WDM = - 0.26 (95% CI: [-0.44; -0.09]), p <0.003
- at 24 weeks WMD = - 0.57 (95% CI: [-0.85; -0.29]), p <0.001

According to the pooled analysis of available data at 24-26 weeks for studies already considered in 2004, a statistically significant difference between donepezil and placebo was found: SMD=0.38 (95% CI: [0.27; 0.48]), p<0.001 (figure 19).

EFFECT ON QUALITY OF LIFE: no new data.

EFFECT ON DEFERRING ADMISSION INTO AN INSTITUTION: not established.

REDUCTION IN MORTALITY: not established.


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Conclusion:

A summary of the main results from the comparative studies versus placebo can be found in figures 20, 21 and 22. New clinical data confirm a statistically significant effect for donepezil compared with placebo on cognitive and functional issues and in the Clinical Global Impression.

The size of this effect is small and the clinical relevance is questionable, especially since the management of missing data in some studies has led to an overestimation of the effects of donepezil.

There is no evidence that donepezil has more of an effect than the placebo on behavioural issues or the quality of life of patients or their carers.

It is still not known whether donepezil slows down the progression of the disease, or if it is likely to delay the admission to a healthcare institution. The impact on the reduction in mortality has not been established.

The duration of the clinical studies is too limited (around six months) in relation to the five years or more during which the patients are likely to receive medication; the question regarding the level of efficacy beyond six months of treatment has been raised.

B. GALANTAMINE (REMINYL)

B.1. Summary of available data

B.1.1. Reminder of the re-assessment opinion conclusions of 20 June 2007

The profile of patients included in the studies used in the Cochrane meta-analysis was similar to those of patients included in the studies evaluating Alzheimer's disease treatments: mainly patients treated as out-patients with a mild to moderately severe form of the disease.

For these patients, this meta-analysis confirmed in studies lasting three to six months that galantamine was more effective than placebo on cognitive function (difference of three points on the ADAS-Cog scale after six months of treatment) and the Clinical Global Impression. Clinical data allowing the impact on daily activities and behavioural issues to be determined are limited. The size of the effect observed was comparable to that highlighted with rivastigmine or donepezil. The clinical benefit highlighted was modest.

Although there was no statistically significant dose-response effect, dosages higher than 8 mg/day were those in which the main statistically significant results were observed.

- Given the methodological limitations, the results from the follow-up (extension phases) or historical comparison studies did not allow the medium- or long-term benefits (beyond 6 months) of galantamine to be determined.
- The efficacy of galantamine in patients who have developed a severe form of Alzheimer's disease (outside of Marketing Authorisation) was not evaluated.

Further studies will be necessary in order to better assess the clinical impact of galantamine on daily activities, behavioural issues and the workload of carers, and also to confirm that the dose of 16 mg/day is one that has the most favourable risk/benefit ratio.

Assessments carried out on longer administration periods (beyond six months) and for more representative patients (see study non-inclusion criteria) of the patient population also appear necessary. Currently, there are no studies that will allow the place and the benefit of galantamine compared to other AChEIs and/or memantine to be determined.

NB. The Cochrane meta-analysis carried out in 2006 has not been updated.

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B.1.2. New clinical efficacy data

Summary of the PenTAG report (NICE 2011)

The studies considered\textsuperscript{26-27,28-29,30-31} by NICE in 2004 were taken in to account during the re-assessment in 2007 by the Committee.

Three new randomised clinical studies versus placebo were used\textsuperscript{32-33,34}. Their study plan, the patient characteristics and an assessment of their internal validity are presented in this report (see tables 9, 10 and 11).

\textbf{EFFECTS ON COGNITIVE FUNCTION:}

In 2004, according to six published studies, galantamine appears to have a statistically significant advantage for patients in terms of cognitive function on the ADAS-cog scale compared with placebo. The size of the effect varies based on the dose of galantamine, with a difference in favour of galantamine of 1.3 points for 8 mg/day, 3.1 points with 16 mg/day, 1.7 points with 18 mg/day, 2.5 to 2.8 points with 16 or 24 mg/day, 1.7 to 3.4 points with 24 to 32 mg/day and 2.3 points with 36 mg/day. In addition, there were more "responding" patients, defined by an improvement of four points or more on the ADAS-Cog scale, (from 14 to 17%) amongst those receiving galantamine than those on the placebo.

The efficacy results from the three studies on cognitive function are described in table 12. They confirm the superior effect of galantamine compared with the placebo on the ADAS-cog scale up to 26 weeks, with the understanding that the analysis of missing data by the LOCF or OC methods tended to overestimate the effect of galantamine.

The meta-analysis taking into account all of the results on cognitive function from available studies confirms the significant effect of galantamine (≤ 24 mg/day) compared with placebo on the ADAS-Cog scale (see figures 23 and 24):

- at 12-16 weeks: WMD = -2.39 (95% CI: [-2.80; -1.97]), p <0.001.
- at 21-26 weeks: WMD = -2.96 (95% CI: [-3.41; -2.51]), p <0.001.

IMPACT ON EVERYDAY ACTIVITIES:

In 2004, the assessment of the effects of rivastigmine was based on the results from:

- three studies showing a slower deterioration on the DAD scale for patients receiving 24-32 mg/day of galantamine than those on the placebo.
- two studies showing a slower deterioration on the ADSC-ADL scale in patients receiving 16 mg/day and/or 24 mg/day of galantamine than those on the placebo.

A favourable benefit of galantamine compared with placebo was found in the three new studies taken into consideration (see table 13).

The meta-analysis taking into account all of the results from available studies confirms the significant functional effect of galantamine (≤ 24 mg/day) compared with placebo:

ADCS-ADL (see figures 25 and 26):
- at 12-13 weeks: WMD = 1.39 (95% CI: [0.59; 2.20]), p <0.001.
- at 21-26 weeks: WMD = 2.23 (95% CI: [1.33; 3.14]), p <0.001.

DAD (see figure 27):
- at 21-26 weeks: WMD = 3.76 (95% CI: [1.66 ; 5.86]), p <0.001.

The pooled analysis of all studies including the results at 21-26 weeks on the impact on functional capability also confirms a superior effect for galantamine (all doses) compared with placebo: SMD=0.27 (95% CI: [0.18; 0.34]), p<0.001 (figure 28; Appendix 6).

EFFECTS ON BEHAVIOURAL ISSUES:

In 2004, the assessment of the effects of galantamine based on the results of three studies showed an improvement, or less of deterioration in the NPI scale for patients receiving 16 mg/day of galantamine than those on the placebo.

Among the new studies, only one reported data: no significant difference in behaviour on the NPI scale between the placebo and the galantamine arms was highlighted in the study by Brodaty et al (see table 14).

The meta-analysis, taking into account all the available results from studies on the NPI scale, confirms the significant effect of galantamine compared with the placebo (all doses) at 21-26 weeks: WMD = - 1.46 (95% CI: [-2.59; -0.34]), p = 0.012, but not at 13 weeks (see figures 29 and 30).

EFFECT BASED ON OVERALL ASSESSMENT (CLINICAL GLOBAL IMPRESSION OF CHANGE):

In 2004, in six studies including measurements using the CIBIC-Plus scale, a superior effect of galantamine compared with placebo was highlighted: an improvement was reported in more patients receiving galantamine (from 0 to 6.5%); conversely, the proportion of patients deteriorating was greater on the placebo (from 4 to 18%). More patients considered as responding had received galantamine: from 4% (8 mg/day) to 17% (24 mg/day). However, meta-analysis of these studies does not enable these results to be confirmed.

The results from the two new studies using the CIBIC scales contradicted each other: results were favourable towards galantamine in the Rockwood et al reference study but not in the Brodaty et al reference study (see table 15).
The meta-analysis of available studies showed a significant effect for galantamine compared with placebo on the CIBIC-plus scale at 26 weeks:

CIBIC-Plus (figure 31): WDM = -0.20 (95% CI: [-0.30, -0.09]), p <0.001.

- **EFFECT ON QUALITY OF LIFE:** no data.
- **EFFECT ON DEFERRING ADMISSION INTO AN INSTITUTION:** not established.
- **REDUCTION IN MORTALITY:** not established.

**Conclusion:**

A summary of the results of the three different comparative studies versus placebo can be found in figures 32 and 33.

The new studies confirm the effect of galantamine compared with placebo, primarily on cognitive function and the impact on everyday activities:

- The size of the effect on cognitive function measured on the ADAS-cog scale is more marked at 21-26 weeks WMD = -2.96 (95% CI: [-3.41; -2.51]), p<0.001 than at 12-16 weeks (WMD = -2.39: 95% CI: [-2.80; -1.97]), p<0.001.

- The effect on functional capability is more significant on galantamine than on the placebo at 21-26 weeks on the ADCS-ADL, (WMD = 2.23 (95% CI: 1.33; 3.14), p<0.001 and DAD scales, WMD = 3.76 (95% CI: [1.66; 5.86]), p<0.001.

Furthermore, the meta-analysis of the results on the NPI scale at 21-26 weeks showed a more significant effect on behaviour for galantamine than for the placebo (WMD = -1.46 (95% CI: [-2.59; -0.34]), p= 0.012, but not at 13 weeks.

The effect of galantamine compared with placebo according to the Clinical Global Impression of change was assessed on the CIBIC plus scale in two new studies; galantamine was only more effective than the placebo in one of these studies. The meta-analysis showed a significant effect of galantamine compared with the placebo at 26 weeks (WMD = -0.20 (IC 95%: [-0.30; -0.09]), p<0.001, (≤ 24 mg/day).

The clinical relevance of these effects remains under question, given their size and knowing that the management of missing data (based on LOCF or OC methods) in these studies had a tendency to over estimate the effect in favour of galantamine.

It is not known whether galantamine slows down progression of the disease, or if it is likely to delay admission to a healthcare institution. The impact on the reduction in mortality has not been established.

The duration of the clinical studies is too limited (around six months) in relation to the five years or more during which the patients are likely to receive medication and the question regarding the level of efficacy (size of the effect) beyond six months of treatment has been raised.
C. RIVASTIGMINE (EXELON)

C.1. Summary of available data

C.1.1. Reminder of the re-assessment opinion conclusions of 20 June 2007

A Cochrane meta-analysis\(^{35}\) investigated all the randomised rivastigmine studies versus placebo available on 13 September 2005. These data confirmed that, for patients with a probable Alzheimer’s disease diagnosis at the mild to moderate stage, rivastigmine had more of an effect than the placebo on cognitive function and everyday activities after 26 weeks of treatment at a dose of 6 to 12 mg/day. Likewise, fewer patients were classified with a more severe stage after treatment with rivastigmine. At a dose of between 1 and 4 mg/day, efficacy was only observed for cognitive function (difference of two points after six months of treatment on the ADAS-Cog scale).

The size of the effect was modest and the question of clinical relevance of the effects observed was raised, although the follow-up period for the randomised studies that compared rivastigmine to placebo was limited to six months.

This meta-analysis did not answer the following questions: the influence of the administration regimen in the reduction in occurrence of adverse effects, the benefit in dividing the dosage over more times during the day (taken three times instead of twice for example) or based on other methods, the efficacy of rivastigmine beyond 6 months of treatment and the clinical relevance of the effects observed.

C.1.2. New clinical efficacy data

No other randomised comparative rivastigmine study versus placebo was presented.

Summary of the PenTAG report (NICE 2011)

Three different randomised clinical study versus placebo were taken into consideration.\(^{36,37,38}\)

Their study plan, the patient characteristics and an assessment of their internal validity are presented in this report (see tables 17, 18 and 19).

The studies considered\(^{39,40,41,42}\) by NICE in 2004 were taken into account during the re-assessment in 2007 by the Committee.


EFFECTS ON COGNITIVE FUNCTION:

In 2004, the significant differences in favour of the rivastigmine (6 - 12 mg/day) arm were highlighted in two out of three studies published, on the ADAS-cog and MMSE scales.

The efficacy results from the three new studies on cognitive function are described in table 20. A dose-dependant effect in favour of rivastigmine was observed, the effect being at its maximum at doses higher than 12 mg/day of rivastigmine. Intention-to-treat analysis was only carried out for one of these three studies (Feldman HH et al, 2007).

The meta-analyses, taking in to account all the cognitive function results (ADAS-Cog and MMSE scales) in the available studies, show a significant effect for 12 mg/day of rivastigmine compared with placebo at 24-26 weeks:

- ADAS-Cog: WMD = -2.46 (95% CI: [-3.37; -1.56]), p <0.001.
- MMSE: WMD = 1.02 (95% CI: [0.63; 1.41]), p <0.001.

The pooled analysis of all the studies including cognitive function results also confirms the superiority of rivastigmine compared with placebo: SMD = 0.28 (95% CI: [0.14; 0.42]), p<0.001 (figure 36; Appendix 6).

IMPACT ON DAILY ACTIVITIES:

In 2004, the assessment of the effects of rivastigmine was based on the results from two studies using the PDS scale. In one of these studies, 6-12 mg/day of rivastigmine was more effective than the placebo; in the other, a more significant proportion of patients in comparison with the placebo saw an improvement of at least 10% in PDS in patients receiving 6-12 mg/day of rivastigmine.

A favourable benefit of rivastigmine on the PDS scale was highlighted at 26 weeks in the Feldman study and at 12 weeks on the ADCS-ADL scale (in the Mowla study (see table 21).

The meta-analysis of available results for the PDS scale showed a significant effect for rivastigmine compared with placebo at 24-26 weeks: WMD = 3.10 (95% CI: [1.81; 4.40]), p=0.001 (figure 37).

The pooled analysis of all studies including results at 24-26 weeks on the functional consequences confirms a superior effect for rivastigmine compared with placebo: SMD = 0.21 (95% CI: [0.12; 0.29]), p<0.001 (figure 38; Appendix 6).

EFFECTS ON BEHAVIOURAL ISSUES:

In 2004, no benefit in favour of rivastigmine compared with placebo was highlighted in the studies examined.

Two other studies measured the effect treatment had on behaviour: in one (Mowlal et al, 2007), with very few participants, the favourable effect of rivastigmine was highlighted, but this favourable effect for rivastigmine was not seen in the other (Winblad et al, 2007) (see table 22).

Due to the heterogeneity of the data available, pooled analysis cannot be carried out.
EFFECT BASED ON OVERALL ASSESSMENT (CLINICAL GLOBAL IMPRESSION OF CHANGE):

In 2004, the available studies including measurements using the CIBIC-Plus scale, highlighted the superiority of 6-12 mg/day of rivastigmine compared with placebo. In one study, there were more patients responding with rivastigmine. In another study, a larger proportion of patients receiving 6-12 mg/day of rivastigmine had a favourable overall assessment on the CIGIC scale (from one to two points). In two studies, a more significant improvement in GDS score was also observed for rivastigmine 6-12 mg/day.

The two new studies investigating the CIBIC-plus and GDS scales have provided contradictory results: they were in favour of rivastigmine in the Feldman study but in the Winblad study, there was no difference between rivastigmine and placebo observed (see table 23).

The meta-analysis of the studies available showed a significant effect for rivastigmine compared with placebo on the CIBIC-plus and GDS scales at 26 weeks:
- CIBIC-Plus (figure 39): WDM = -0.42 (95% CI: [-0.55, -0.29]), p < 0.001.
- GDS (figure 40): WDM = 0.20 (95% CI: [0.12; 0.27]), p < 0.001.

The pooled analysis of the study results that evaluated the effect of treatment based on the clinical global impression confirms the effect in favour of rivastigmine at 24-26 weeks of treatment: SMD = 0.23 (95% CI: [0.16; 0.31]), p < 0.001 (see: figure 41).

EFFECT ON QUALITY OF LIFE: no data.

Conclusion:

A summary of the results from the three new comparative studies versus placebo can be found in figure 42. The new studies essentially confirm the short-term (< 14 weeks) effect of rivastigmine compared with placebo on cognitive issues, measured using the MMSE and ADAS-cog scales.

At 24-26 weeks, there was a small benefit in favour of rivastigmine: WMD = -2.46 (95% CI: [-3.37; -1.57]), p < 0.001 only highlighted in dosages greater than 12 mg/day.

The clinical relevance of these effect remains in doubt. Especially since the management of missing data (based on LOCF or OC methods) in some studies has led to an overestimation of the effects in favour of rivastigmine.

The meta-analysis confirms that rivastigmine is superior to placebo in terms of the impact on functional capability at 24-26 weeks: WMD = 3.10 (95% CI: [1.81; 4.40]), p = 0.001. The size of this effect is modest.

Available data does not allow the superiority of rivastigmine to be clearly confirmed compared with placebo in terms of overall assessment, as it is dependent on the scale used (CIBIC-plus vs. ADSC-GIC or GDS). At best, the size of the effect would appear to be very low (CIBIC-plus WMD = -0.42 95% CI: [-0.55; -0.29]), p < 0.001; GDS: WMD = 0.20 95% CI: [0.12; 0.27]), p <0.001).

The effect of rivastigmine in comparison with placebo on behavioural issues and the quality of life of the patient or carers was not established.
It is not known if rivastigmine slows down the progression of the disease, or if it is likely to delay admission to a healthcare institution. The impact on the reduction in mortality has not been established.

According to results from one study, the transdermal delivery of 9.5 mg/day of rivastigmine is safer and more effective than an oral dose of 12.5 mg/day of rivastigmine.

The duration of the clinical studies is too limited (around six months) in relation to the five years or more during which the patients are likely to receive medication: what is the efficacy (size of the effect) beyond six months of treatment likely to be?
NMDA receptor antagonists

D. Memantine (EBIXA)

D.1. Summary of available data

D.1.1. Reminder of the conclusions of data already considered by the Transparency Committee (opinion of 20 June 2007):

D.1.1.1. For moderately severe to severe stages of the disease (MMSE < 15)

During the first assessment of EBIXA by the Transparency Committee (opinion of 4 December 2002), demonstration of efficacy was based on the results from two studies (studies 9403 and 9605) which compared 10 to 20 mg/day of memantine with placebo, mainly in patients with a severe form of the disease. One of these studies concerned institutionalised patients (study MRZ 9403), while in the other the patients were treated as out-patients (pivotal study 9605):

- The short-term MRZ 9403 study only concerned a limited number of patients. The differences observed in favour of memantine and in comparison with placebo were slight.
- In study 9605, memantine contributed to a significantly slower deterioration in activities of daily living and decline in cognitive function for patients. The response rate at six months (significant improvement or stabilisation observed for 29% of patients treated with memantine versus 10% of patients treated with placebo) appears to confirm the favourable results observed "on average" for everyday activities and on the Clinical Global Impression. Very few adverse effects were reported. The data taken into consideration were limited (small number of participants and short duration of study). The specific effect linked to treatment (reduced response to treatment compared with response to placebo) varied from 5% (responder 1) to 19% (responder 2) according to the treatment response definition criteria. The size of the effect, determined by the variation in scores from the different scales, was modest over the time period considered. No comparative data versus a reference treatment was presented.

During the re-assessment in 2007, two new clinical studies versus placebo were taken into consideration:

- the results from the MD-0145 study did not highlight a clinical benefit of memantine compared with placebo on the cognitive (SIB score) and functional (ADCS-ADL score) domains after six months of treatment in these patients.
- the MD-0246 study was the first randomised study published that compared the benefit of combining several medicinal products in the treatment of patients with a moderately severe to severe form of the disease. A greater efficacy for the combination of memantine 20 mg/day + donepezil 10 mg/day versus 10 mg/day of donepezil monotherapy on the cognitive, global and functional domains in out-patients after six months of treatment was observed. However, numerous efficacy endpoints were evaluated (risk of increase in alpha risk). The differences observed between the two groups of patients were only modest: 3.4 points on a scale of 100 points for SIB for

example. The study duration was limited to six months despite the disease evolving over several years. The tolerance of this combination was good during this period. The question of the clinical relevance of a therapeutic strategy that combined these two medicinal products (or more generally an AChEI and memantine) was raised, both from a regulatory and relevance point of view. The SPC for the medicinal products does not raise the question of combinations. The results from this study, favourable for dual therapy, were highlighted previously by certain experts to justify their prescription for certain patients. The size of the effects observed was modest, despite the combined pharmacological action of the two main ingredients. A single study (conclusive) was carried out for this stage of severity of the disease; another study carried out with this same combination was inconclusive, but for patients with a less severe form of the disease. A further study would therefore be useful to confirm (or not) the benefit of this (new) potentially useful therapeutic option for some patients, and to measure its long-term clinical impact, in terms of both efficacy and safety.

According to a Cochrane meta-analysis, the statistically significant effects in favour of memantine in comparison with placebo were highlighted in several domains (cognitive function and the impact on activities of daily living). In addition, patients on memantine were less frequently agitated than those on placebo. It is not possible to appreciate the role of memantine in comparison with medicinal products with an anticholinesterasic effect, in the absence of a comparative study. The size of the effect observed in comparison with placebo appeared to be small to modest in the controlled clinical studies. Memantine was safe to use.

The Committee concluded that “for patients with a moderately severe (MMSE < 15) to severe (MMSE > 3) form of Alzheimer's disease, after 24 to 28 weeks of treatment, the statistically significant effects in favour of memantine at a dosage of 20 mg/day were highlighted in several domains (in particular, cognitive function and the impact on activities of daily living), compared with placebo. In addition, the frequency of incident agitation was lower in patients treated with memantine than those on the placebo. The size of the effect in comparison to placebo appeared to be small to modest in the controlled clinical studies for these patients. Memantine was very safe. It is not possible to appreciate the role of memantine, in comparison with other medicinal products with an anticholinesterasic effect, in the absence of a comparative study for moderately severe forms. Memantine (EBIXA) is also indicated in severe stages of the disease. It is possible that certain patients (not identifiable before treatment) would see an additional benefit of the combination of memantine and donepezil compared with treatment with donepezil alone. The size of the effect is small to modest. This new therapeutic option recommended by some experts (but not formally validated by a Marketing Authorisation for the two medicinal products) is based on the results of a single clinical study. No benefit was seen by patients included with a less severe stage in another comparative study versus placebo (MD-12 study).”

**D.1.1.2. For moderate forms**

Two clinical studies compared the efficacy and tolerance of memantine (EBIXA) against those of a placebo over six months (24 weeks) in patients treated on an out-patient basis included with a mild (outside of scope of Marketing Authorisation) or moderate form of Alzheimer's disease (MMSE score of between 10 and 22 in the MD-10 study; score between 11 and 23 in study 99679). A pooled analysis of these two studies, taken into consideration by the EMA, was proposed. A third study MD-12 lasting 24 weeks compared the combination of memantine + donepezil versus placebo for the same stages of severity.

Two meta-analyses were taken into consideration:

- one concerned six comparative studies versus placebo lasting six months, carried out on patients treated on an out-patient basis with a moderate to severe form of Alzheimer’s

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disease (MMSE score < 20). These were studies MRZ-9605,48 MD-01,49 MD-1050 and 9967951 (monotherapy) and studies MD-0252 and MD-1253 for patients also treated with acetylcholinesterase inhibitors (dual therapy).

- the other was a Cochrane54 analysis, which took into account studies that evaluated memantine for patients with a mild to severe form of Alzheimer's disease. Also taken into consideration were the Ditzler 1991,55 Gortelmeyer 199256 and Pantev 199357 studies.

The Committee concluded that "the efficacy and tolerance of memantine were evaluated based on the results from three randomised clinical studies versus placebo, two carried out as monotherapy and one in combination with donepezil. The assessment was carried out over a treatment period that did not exceed six months. Memantine had more of an effect than the placebo on cognitive function and the Clinical Global Impression in only one of these studies. This effect was confirmed by Cochrane meta-analysis, but with a benefit qualified as "marginal" on the evolution of cognitive disorders and the overall assessment. No impact on the behaviour of patients or on the assessment of their capability of carrying out activities of daily living was observed. The efficacy of memantine appears to be of the same order of magnitude as those found with anticholinesterasic medicinal products. According to the conclusions of several reports carried out recently,58,59 the prescription of memantine to patients at this stage of severity of the disease (except as part of clinical studies) is not recommended. Undertaking a clinical study to compare the efficacy and the adverse effects of memantine with those of other anticholinesterasic medicinal products (donepezil, galantamine, and rivastigmine) would be possible, ethical and beneficial (see scientific discussion of the EMEA report). This is especially the case since the benefit of combining memantine with an acetylcholinesterase inhibitor has not been established for this stage of severity of the disease, based on the results from study MD-12."

D.1.2. New clinical efficacy data

Summary of the PenTAG report

The report states that the assessment team did not use the analysis methods proposed by the Lundbeck laboratory when pooling the data for the studies that compared memantine with placebo for those prescribed as a monotherapy or in combination with an AChEI, due to the heterogeneity of this data. Nevertheless, the results from this method are presented in

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Appendix 14, for information only. This analysis method is biased due to the fact it favours the results in favour of memantine.

Since 2004, a new randomised clinical study (MD-01, van Dyck et al, 2007) versus placebo was taken into consideration. The study design, the patient characteristics and an assessment of the internal validity are presented in the PenTAG report (tables 25, 26 and 27).

Results
Results of the meta-analysis taking into account the new data:

- **EFFECTS ON COGNITIVE FUNCTION:**

  In 2004, meta-analysis of two studies (MD-02/Tariot 2004 and 9605/Reisberg 2003), which used the Severe Impairment Battery (SIB) scale to measure the effects on cognitive function, showed a significant effect of memantine compared with placebo. However, the degree of deterioration according to the MMSE scale was not different between the two arms.

  The MD-01 study comprised of six analyses using the SIB scale; according to one for these (at 12 weeks) a significant effect with memantine was observed. This effect was poorly established by repeated measures (see table 28).

  According to the meta-analysis of studies 9605 and MD-01, memantine had more of an effect than the placebo after 12 weeks on the SIB scale: WDM = 4.15 (95% CI: 0.52, 7.78), p = 0.025, but not after 24-28 weeks (figures 43 and 44).

- **IMPACT ON ACTIVITIES OF DAILY LIVING:**

  In 2004, memantine had more of an effect than the placebo on the Alzheimer’s Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) scale in both the 9605 and MD-02 studies (co-therapy).

  No difference was highlighted between the memantine and placebo arms according to the results from the MD-01 study (table 29).

  According to the meta-analysis of both the 9605 and MD-01 studies on the ADCS-ADL scale (19 items): no difference was highlighted between the memantine and placebo arms at 12 weeks. The difference in favour of the memantine arm is marginally significant after 24-28 weeks, knowing that the analysis was carried out using the LOCF technique which tends to favour memantine: WMD = 1.41 (95% CI: 0.04; 2.78), p = 0.044 (see figures 45 and 46).

  However, it should be noted that another meta-analysis was carried out using data from the Functional Assessment Staging Tool (FAST) scale at 24-28 weeks of treatment. A significant effect for memantine compared with placebo was highlighted: WMD = - 0.34 (95% CI: -0.55, -0.13), p = 0.002 (figure 47).

- **EFFECTS ON BEHAVIOURAL DISORDERS AND MOOD DISORDERS:**

  In 2004, meta-analysis concluded that it would appear that patients receiving memantine and a regular dose of donepezil had, on average, a lower NPI score than those on the placebo. As a monotherapy, no statistical difference between the two arms was highlighted.

  The MD-01 study evaluated the effects on the NPI and behaviour of geriatric patients (BGP) scales. No statistical difference between the two arms was highlighted on these two scales (table 30).
According to the meta-analysis of studies 9605 and MD-01, there was no difference between the memantine and the placebo arm on the NPI scale at 24-28 weeks of treatment (figure 48).

- **EFFECT BASED ON OVERALL ASSESSMENT (CLINICAL GLOBAL IMPRESSION OF CHANGE):**

  In 2004, memantine had more of an effect than placebo on the Clinician Interview-Based Impression of Change (CIBIC-Plus) scale in both the MD-04 (dual therapy) and 9605 studies.

  In the MD-01 study, no difference between the memantine and placebo arms was highlighted on this scale (table 31).

  According to the meta-analysis of studies 9605 and MD-01, a significant effect of memantine compared with placebo was highlighted: WMD = -0.30 (95% CI: -0.47, -0.13), p <0.001 (figure 49).

- **EFFECT ON QUALITY OF LIFE:** no data available.

- **EFFECT ON DEFERRING ADMISSION INTO AN INSTITUTION:** not established.

- **REDUCTION IN MORTALITY:** not established.

**Conclusion:**

A summary of the results from the retained comparative studies versus placebo can be found in figure 50.

Another randomised study comparing memantine with placebo was identified; its quality was average to poor.

- Regarding cognitive function, meta-analysis showed an effect in favour of memantine on the SIB scale after 12 weeks of treatment [WMD= -0.34 (95% CI: 0.52, 7.78) = 0.025] but not after 24 weeks of treatment.
- Regarding the impact on functional capability, an effect in favour of memantine was highlighted on the FAST scale, but not on the ADCS-ADL scale (at 12 weeks) in this other study.
- The meta-analysis confirms this result: ADM = -0.34 (95% CI: -0.55; -0.13), p = 0.002.
- A marginal advantage in favour of memantine was highlighted by meta-analysis of the ADCS-ADL scale, only at 24-28 weeks: ADM = 1.41 (95% CI: 0.04; 2.78) p = 0.044.
- Behavioural issues: memantine does not have more of an effect than the placebo.
- Clinical Global Impression: meta-analysis highlighted an effect in favour of memantine: WMD = -3.00 (95% CI: -0.471; -0.129), p <0.001.
- No study reported on the results in terms of quality of life.

In conclusion, the studies were judged as being of average to poor quality. Meta-analysis of memantine studies (monotherapy) versus placebo highlighted a benefit in favour of memantine after 12 weeks of treatment on the SIB scale, after 24-28 weeks on the impact on functional capability according to some measurement methods, and according to the Clinical Global Impression. Memantine does not appear to be more effective than placebo for behavioural issues.

It is not known if memantine slows down the progression of the disease or if it is likely to delay admission to a healthcare institution. The impact on the reduction in mortality has not been established.

The duration of these clinical studies is too limited (about six months) in relation to five years or more during which the patients are likely to receive medication: what is the efficacy (size of the effect) beyond six months of treatment likely to be?