HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 June 2007

EBIXA 10 mg, film-coated tablets
Box of 56 tablets: CIP: 359 553-1
Box of 100 tablets: CIP: 564 933-7

EBIXA 10 mg, oral drops, solution
Bottle 50 g: CIP: 359 556-0

Applicant: LUNDBECK

Memantine hydrochloride

List I
Drugs available on restricted medical prescription:
- initial annual prescription by doctors specialised in neurology or in psychiatry, by specialist doctors with a complementary certificate in geriatrics and by specialist or general doctors qualified in gerontology.
- medicinal product requiring specific monitoring during treatment

Date of the initial MA (centralised European procedure): May 15, 2002.
Date of last revisions to MA: November 15, 2005 (extension of indication granted by the EMEA for the treatment of patients with a moderate form of Alzheimer's disease) and April 27, 2006.

Reason for request :
Change in the conditions of inclusion: inclusion on the list of medicines reimbursed by National Insurance (B/56 and oral solution) and approved for hospital use (for all pack sizes) in the extension of indication in patients with a moderate form of Alzheimer's disease.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Memantine (hydrochloride)

1.2. Indication

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

(Reminder: previous description of indication: treatment of patients with moderately severe to severe Alzheimer's disease.

1.3. Dosage

Therapy should only be started if a carer is available who will regularly monitor drug intake by the patient.

Adults: The maximum daily dose is 20 mg. In order to reduce the risk of adverse effects, the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

- treatment should be started with 5 mg daily (half a tablet/10 drops in the morning) during the 1st week.
- in the 2nd week 10 mg daily (half a tablet/10 drops twice a day).
- in the 3rd week 15 mg daily (one tablet/20 drops in the morning and half a tablet/10 drops in the afternoon) is recommended.

From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg daily (one tablet/20 drops twice a day).

Elderly: on the basis of the clinical studies, the recommended dose for patients over the age of 65 years is 20 mg daily (10 mg twice daily) as described above.

Children and adolescents under the age of 18 years: the safety and efficacy of memantine in children and adolescents have not been demonstrated.

Renal impairment:

- In patients with normal or mildly impaired renal function (creatinine clearance up to 130 µmol/l maximum): no dosage reduction is required
- In patients with moderate renal impairment (creatinine clearance 40 to 60 ml/min/1.73m^2). the daily dose should be reduced to 10 mg.
- In patients with severe renal impairment: no data is available.

Hepatic impairment: No data is available on the use of memantine in patients with hepatic impairment.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

N : Nervous system
N06 : Psychoanaleptics
N06D : Anti-dementia drugs
N06DX: Other anti-dementia drugs
N06DX01 Memantine

2.2. Medicines in the same therapeutic category

In the moderate forms of the disease: none.

NB: Memantine (EBIXA) is an N-methyl-D-aspartate receptor antagonist, which distinguishes it by its action mechanism from cholinesterase inhibitors.

2.3. Medicines with a similar therapeutic aim

- acetylcholinesterase inhibitors (anticholinesterase drugs) indicated for treating the symptoms of **mild** to **moderately severe** Alzheimer's disease.

- donepezil (ARICEPT)
- galantamine (REMINYL and REMINYL PR)
- rivastigmine (EXELON)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy data for the moderate forms of the disease:

The laboratory presented the following results:

Three placebo-controlled comparative studies during six months in patients with a mild to moderate form of the disease (baseline MMSE score between 10 and 23):

- Monotherapy: studies MD-10/Peskind 2004 and 99679
- Bitherapy with donepezil (ARICEPT): study MD-12

A pooled analysis of the MD-10/Peskind 2004 and 99679 studies is presented.

A meta-analysis of 6 placebo-controlled comparative studies lasting 6 months carried out on outpatients with moderate to severe Alzheimer's disease (MMSE score < 20). These are studies MRZ-9605, MD-01, MD-10 and 99679 (monotherapy) and studies MD-02 and MD-12 of patients also treated by acetylcholinesterase inhibitors (bitherapy).

A meta-analysis of the Cochrane group of studies which evaluated memantine in patients with mild to severe Alzheimer's disease[1].

Table 1: Methodology of the placebo-controlled comparative clinical studies available with mild to moderate forms of the disease

Study	Baseline MMSE level	Design	Number of randomised patients:	Primary efficacy endpoints
Phase III clinical studies of outpatients with mild to moderate forms of the disease				
MD-10	10-22	Multi-centre, double-blind, randomised, placebo-controlled study (monotherapy) 24 weeks	403 PBO: 202 MEM: 201	ADAS-cog CIBIC-plus ADCS-ADL_{23} NPI
99679	11-23	Multi-centre, double-blind, randomised, placebo-controlled study (monotherapy) 24 weeks	470 PBO: 152 MEM: 318	ADAS-cog CIBIC-plus ADCS-ADL_{23} NPI
MD-12	10-22	Multi-centre, double-blind randomised, placebo-controlled study (bitherapy) (patients treated with donepezil, rivastigmine or galantamine) 24 weeks	433 PBO: 216 MEM: 217	ADAS-cog CIBIC-plus ADCS-ADL23 NPI

Source: LUNDBECK

[1] McShane R, Areaosa Sastre A, Minakaran N. Memantine for dementia. The Cochrane Database of Systematic Reviews 2006, Issue 2. Art. N0 :CD003154.pub5.

Summary of randomised placebo-controlled comparative studies

3.1.1. Results from the studies MD-10 and 99679

Two clinical studies compared the efficacy and safety of memantine (EBIXA) *versus* placebo for 6 months (24 weeks) in outpatients included at a mild or moderate stage of Alzheimer's disease (MMSE score between 10 and 22 in study MD-10; score between 11 and 23 in study 99679).

The methodology used in these studies was comparable. To be included in the study, patients had to meet the following main criteria:

- Be at least 50 years of age
- Have a probable diagnosis of Alzheimer's disease confirmed according to the NINCDS-ADRDA and DSM-IV-TR criteria (study 99679)
- Present a probable diagnosis of Alzheimer's disease, consistent with the results from a scan or MRI carried out during the last 12 months
- Have a modified HIS score ≤ 4
- Have a MADRS[2] score < 22 (study MD-10)
- Patients who had previously been treated with an acetylcholinesterase inhibitor had to have discontinued their treatment at least 1 month before inclusion.

Patients who completed the 24 weeks had the opportunity to continue their treatment in an optional, open-label, non-comparative extension phase[3].

The primary efficacy endpoint was the progression of the ADAS-cog score (assessment of cognitive functions) and CIBIC-plus score (global assessment of the patient) from the time of inclusion to the end (week 24) of the study.

The progression over six months of the ADCS-ADL score (assessment of functional capacities) and the NPI score (assessment of behavioural disorders) were secondary endpoints.

Responder patients were defined as those with a cognitive improvement considered clinically relevant (reflected by an improvement in the ADAS-cog score of ≤ -4) and an improvement or stabilisation in the score for the global rating (CIBIC-plus ≤ 4).
These efficacy endpoints were evaluated at the time of inclusion and after 1 month, 2 months, 3 months, 18 weeks and 6 months of treatment.

Results of study MD-10

After a pre-selection period of 1 to 2 weeks where patients received a placebo (simple blind), 201 patients were randomised to the memantine group and 202 patients to the placebo group. The titration period required to reach the 20 mg daily dose of memantine lasted 1 month.

Clinical results after 6 months of treatment

Out of the 403 randomised patients (mean age: 77 to 78; almost 60% were women), 332 patients (82.4%) completed the study (82.7% for the placebo group and 82.1% for the memantine group). Treatment discontinuations were most often linked to the occurrence of an adverse event, which was reported for 5% of patients in the placebo group and 9.5% of patients in the memantine group. The mean baseline MMSE score varied from 17.2 (+/- 3.4) to 17.4 (+/-3.7).
The rates of patients who had previously taken a cholinesterase inhibitor (donepezil, rivastigmine, galantamine) before inclusion were comparable in both treatment groups, ranging between 62 and 69% with a treatment duration of around 5 months (151 days).

[2] MADRS score: Montgomery-Asberg Depression Rating Scale score
[3] Only the results from the comparative and randomised phase of these studies have been taken into account for the results analysis.

The mean daily treatment dose for the memantine group was 17.9 mg.

- Cognition area

Table 2: Results for the ADAS-cog score (ITT population)

ADAS-cog	Placebo		Memantine		Mean difference (least squares)	P
	N	Mean (σ)	N	Mean (σ)		
Baseline value	198	27.3 (9.74)	195	27.2 (11.01)		
Progression W24 (LOCF)	198	1.1 (0.56)	195	-0.8 (0.56)	-1.9	0.003
Progression W24 (OC)	162	1.0 (0.62)	160	-0.0 (0.62)	-1.1	0.130

A mean difference of -1.9 points in the memantine group for ADAS-cog was observed, p=0.003 (LOCF analysis). No difference was highlighted according to the OC analysis (per protocol).

- Global assessment of patients

Table 3: Results for the CIBIC-plus score (ITT population)

CIBIC-plus	Placebo		Memantine		P
	N	Mean (σ)	N	Mean (σ)	
Baseline value	198	3.7 (0.82)	196	3.8 (0.83)	
Value at W24 (LOCF)	197	4.5 (1.06)	196	4.2 (0.96)	0.004
Value at W24 (OC)	166	4.5 (1.08)	164	4.2 (1.00)	0.030

A mean difference of 0.3 points in the CIBIC-plus score in favour of the memantine group was therefore observed, p=0.004. No significant difference was highlighted according to the OC analysis (per protocol).

No significant difference was observed in the memantine group for the ADCS-ADL score. A significant difference in favour of the memantine group was observed for the NPI score after 6 months of treatment (p=0.011).

- Responder analysis

The results based on the response to the treatment varied according to the definition selected:

Table 4: Results of the responder analysis (ITT/LOCF population)

	Placebo	Memantine	p
Cognitive improvement (ADAS-cog ≤ -4)	20%	24%	0.396
Improvement or stabilisation of global assessment (CIBIC-plus ≤ 4)	51%	67%	0.001
ADAS-cog ≤ -4 and CIBIC-plus ≤ 4	20%	14%	0.142

An improvement or a stabilisation of the global area was observed in 67% of patients receiving memantine and in 51% of patients receiving a placebo, p=0.001.

In conclusion, from the MD-10 study results, memantine had more effect than placebo on cognition and the global assessment, after 6 months treatment in patients with mild to moderate Alzheimer's disease.
The superiority of memantine treatment observed in comparison with placebo was slight and this raises the question about its clinical relevance. In the case of almost two-thirds of patients, an improvement or stabilisation of the global assessment score was achieved, but the number of responders for cognition (defined by an ADAS-cog score ≤ -4: 20% with placebo and 24% with memantine, p=0.396) or for the two efficacy endpoints (ADAS-cog ≤ - 4 and CIBIC-plus ≤ 4: 20% with placebo and 14% with memantine, p=0.142) did not differ between the two treatments.

Results of study 99679

After a pre-selection period of 1 to 2 weeks where patients received a placebo (simple blind), 318 patients were randomised to the memantine group and 152 patients to the placebo group. The titration period required to reach the 20 mg daily dose of memantine lasted 1 month.

Results after 6 months of treatment:

Out of the 470 randomised patients (mean age: 73 to 74) 59.9% of women received the placebo and 64.8% memantine, 409 patients (87%) completed the study: 138 (91%) in the placebo group and 271 (85%) in the memantine group. Discontinuation of treatment was most often linked to the occurrence of an adverse event, which was reported for 4% of patients in the placebo group and 9% of patients in the memantine group.

The mean baseline MMSE score was around 19 (18.6 to 18.9). It should be noted that the MMSE scores corresponded to a population of patients with mild to moderate Alzheimer's disease, with a more noticeable distribution towards patients who were mildly affected (Reminder: EBIXA was not indicated for treating the mild stages of Alzheimer's disease).

Previous intake of a cholinesterase inhibitor before inclusion was comparable in the two treatment groups :36% of patients in the placebo group and 38% in the memantine group, with a treatment duration of around 5 months.

- Cognition area

The difference observed between the two treatment groups in the average progression of the ADAS-cog score was not statistically significant.

Table 5: Results for the ADAS-cog score (CS24 population)

ADAS-cog	Placebo		Memantine		Mean difference (least squares)	P
	N	Mean (σ)	N	Mean (σ)		
Baseline value	135	23.9	268	25.5		
Progression at W24	135	-1.08 (0.54)	268	-1.93 (0.41)	-0.85	0.156

- Global assessment of patients (CIBIC-plus score)

No difference was demonstrated in the scores on the CIBIC-plus scale between the two treatment groups.

No significant difference was observed in favour of memantine group for the ADCS-ADL and NPI scores (secondary endpoints) after 6 months of treatment

- Responders analysis

The results based on the response to the treatment varied according to the definition selected:

Table 6: Results of the responder analysis (CS24 population)

	Placebo (n=152)	Memantine (n=318)	p
Cognitive improvement (ADAS-cog ≤ -4)	28%	40%	0.028
Improvement or stabilisation of global assessment (CIBIC-plus ≤ 4)	62%	66%	0.441
ADAS-cog ≤ - 4 and CIBIC-plus ≤ 4	25%	31%	0.246

In conclusion, the results observed in this study carried out on patients being treated at a mild or moderate stage of the disease do not allow a conclusion to be reached as to whether memantine has a greater clinical effect than that of a placebo on the progression of the ADAS-cog (cognition) and CIBIC-plus (global assessment) scores after a 6-month period of treatment.

3.1.2. Results of the pooled analysis of the MD-10 and 99679 studies
(submitted to the EMEA)

Design
A pooled analysis was carried out of the data of the two studies MD-10 and 99679, with the same study plan. It was carried out in patients from the FAS (Full-Analysis Set) population with an OC and LOCF analysis.

Results
Out of the 873 randomised patients (519 in the memantine group and 354 in the placebo group) 741 (85%) completed both studies: 436 (84%) patients in the memantine group and 305 (86%) in the placebo group. The mean age of the patients at inclusion was 75.5 years; women accounted for approximately 60% of the subjects. The average MMSE score was 18. The duration of treatment was around 5 months on average.
The population selected for the analysis was 855 patients (506 in the memantine group and 349 in the placebo group).

- Cognition assessed in terms of progression of the ADAS-cog score
A mean difference between the two treatment groups was observed in favour of patients treated with memantine after 6 months (LOCF: -1.24, p=0.004; OC: -0.91, p=0.049).
But this effect, which is low, has a debatable clinical relevance.

- Global assessment of patients using the CIBIC-plus score
The mean difference observed between the two treatment groups was in favour of patients treated with memantine (LOCF: -0.17, p=0.022; OC: -0.16, p=0.047) after 6 months.
But this effect, which is low, has a debatable clinical relevance.

- In terms of responders
The proportion of patients with an improvement of at least 4 points in their cognitive functions and an improvement or stabilisation in their global assessment and who received memantine (26%) was higher than that for patients with placebo (18%) during the last 3 months of the study (from Week 12 to Week 24), with an observed difference of 8%, $p < 0.05$.

In conclusion, the results of this pooled analysis carried out on patients at a mild to moderate stage of the disease (from studies MD-10 and 99679) show that if memantine had a greater clinical effect than that of the placebo on cognition and global assessment after a 6-month period of treatment, the size of the memantine's effect on these endpoints was small and raises the question of its clinical relevance.

According to post-hoc analyses, it is possible (cf. EPAR) that the memantine's effect was greater in patients most severely affected and in those who had previously received an acetylcholinesterase inhibitor.

Regarding the distribution of patients according to the stage of severity, the supplementary data submitted to EMEA showed that 58 patients (30%) in the study MD-10 and 75 patients (50%) in the study 99679 who had received a placebo were included in the mild stage category (MMSE > 20). In the groups treated with memantine 36% (70 patients) belonged to this category in the study MD-10 and 46.5% (144 patients) in the study 99679.

3.1.3. Results of study MD-12

The purpose of this study was to compare the efficacy and safety of memantine (EBIXA) *versus* placebo during 6 months in outpatients with a mild to moderate Alzheimer's disease (MMSE score between 10 and 22) and who were treated with an acetylcholinesterase inhibitor (bitherapy).

Design

To be included in the study, patients had to meet the following main criteria:

- Be at least 50 years of age
- Have a probable diagnosis of Alzheimer's disease confirmed according to the NINCDS-ADRDA criteria
- Have a modified HIS score ≤ 4
- Have a probable diagnosis of Alzheimer's disease, consistent with the results from a scan or MRI carried out during the last 12 months
- Have a MADRS score < 22
- Have been treated with donepezil, rivastigmine or galantamine during the last 6 months.

Patients who completed the 24 weeks had the opportunity to continue their treatment in an optional, open-label, non-comparative extension phase (MD-12A).

Patients were randomised at the end of a pre-selection period of 1 to 2 weeks when each patient received a placebo. The two treatment groups were then randomised: 217 patients in the group receiving the memantine/acetylcholinesterase inhibitor combination and 215 in the group receiving the placebo/acetylcholinesterase inhibitor combination.
The titration period required to reach the 20 mg daily dose of memantine lasted 1 month.

The primary efficacy endpoint was the progression between inclusion and the end (week 24) of the study, of the ADAS-cog score and CIBIC-plus score.

The ADCS-ADL, NPI, RUD and MMSE after 24 weeks were evaluated as secondary efficacy endpoints.

An analysis of the response to the treatment was conducted. Responders were defined as those with a cognitive improvement (an improvement in the ADAS-cog score of ≤ -4) and an improvement or stabilisation in the score for the global assessment (CIBIC-plus ≤ 4).

Results after 6 months of treatment:
Out of 433 randomised patients in study MD-12, 385 patients (89%) completed the study (88% of patients in the placebo/acetylcholinesterase inhibitor treatment group and 89% in the memantine/acetylcholinesterase inhibitor treatment group). Cases of study discontinuation were most often linked to the occurrence of an adverse event, which was reported for 8% of patients in the placebo/acetylcholinesterase inhibitor group and 6% of patients in the memantine/acetylcholinesterase inhibitor group.

The patients' baseline characteristics were comparable for criteria such as age, gender, weight and level of severity of Alzheimer's disease (MMSE score).
All the patients included in this study continued their treatment with an acetylcholinesterase inhibitor.

Table 7: Previous anti-dementia treatments (safety population)

Previous anti-dementia treatments	Placebo/acetylcholinesterase inhibitor (n=216)	Memantine/acetylcholinesterase inhibitor (n=217)
Donepezil	63.4%	71.0%
Rivastigmine	20.4%	15.2%
Galantamine	16.2%	15.2%

The mean duration of treatment was 155 days in the memantine/acetylcholinesterase inhibitor group and 158 days in the placebo/acetylcholinesterase inhibitor group.
The mean daily treatment dose for the memantine/acetylcholinesterase inhibitor group was 19.5 mg.

- No difference was highlighted between the memantine/acetylcholinesterase inhibitor and placebo/acetylcholinesterase inhibitor groups in terms of cognition (based on the ADAS-cog score) and global assessment (CIBIC-plus). The same was true for each of the secondary endpoints (ADCS-ADL score, NPI score, MMSE score).

Table 8: Results for the ADAS-cog score (ITT population)

ADAS-cog	Placebo/acetylcholi-nesterase inhibitor		Memantine/acetylcholi-nesterase inhibitor		Mean difference (least squares)	p
	N	Mean (σ)	N	Mean (σ)		
Baseline value	212	26.8 (9.88)	212	27.9 (10.98)		
Progression at W24 (LOCF)	213	0.8 (0.45)	214	0.1 (0.45)	-0.7	0.184

Table 9: Results for the CIBIC-plus score (ITT population)

CIBIC-plus	Placebo/acetylcholinesterase inhibitor		Memantine/acetylcholinesterase inhibitor		P
	N	Mean (σ)	N	Mean (σ)	
Baseline value	213	3.89 (0.76)	214	3.93 (0.76)	
Value at W24 (LOCF)	213	4.42 (0.96)	214	4.38 (1.00)	0.843

In conclusion, combining a 20 mg daily dose of memantine with a cholinesterase inhibitor in patients with mild to moderate Alzheimer's disease was not more effective than a placebo for the patients in this study. It has therefore not been established that bitherapy involving a combination of memantine and an acetylcholinesterase inhibitor is more effective than monotherapy with an acetylcholinesterase inhibitor at these stages of Alzheimer's disease.

3.1.4. Results of a meta-analysis of 6 clinical studies carried out on patients at a moderate to severe stage (requested by EMEA, cf. EPAR)

The results observed in the previous studies refered to a population of patients with mild to moderate Alzheimer's disease. The purpose of the meta-analysis was to demonstrate that memantine's efficacy was greater in patients starting the treatment at a moderate stage than in those at a mild stage (where the efficacy did not seem to be any different to that of the placebo).

Design

This analysis was based on 6 placebo-controlled randomised clinical studies lasting 6 months carried out on outpatients, diagnosed at the time of their inclusion as being at a moderate, moderately severe or severe stage of the disease (MMSE score < 20).

Four monotherapy studies were selected (MRZ-9605, MD-01, MD-10 and 99679) and two studies involving patients being treated with an acetylcholinesterase inhibitor at a stable dosage (bitherapy studies MD-02 and MD-12).
The effect size and the number of patients defined as responders were assessed.

- Responder analysis

This analysis was carried out based on two different definitions of the response to the treatment:

Patients with a pronounced clinical worsening were defined as those with:

- ADAS-cog < 4 points or reduction in SIB by 5 points or more
- AND a decrease in the CIBIC-plus score
- AND a decrease in the ADL

Patients with a clinical worsening were defined as those with:

- A decrease in the ADAS-cog or SIB scores
- AND a fall in the CIBIC-plus score
- AND a decrease in the ADL

Results

These results refered to 1,826 patients, where 959 patients received memantine and 867 a placebo.

- Effect size assessment

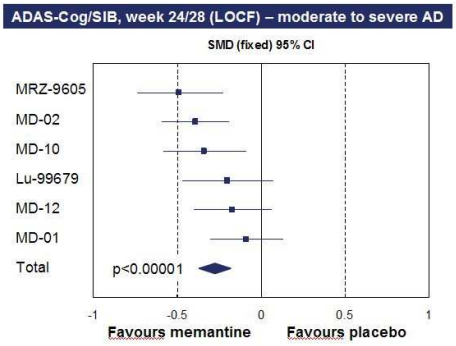
The results for the patients included at a mild stage have not been submitted by the laboratory (cf. accompanying note sent by the laboratory in October 2006).
The tables and diagrams below present the results for cognitive, functional and global assessment after 6 months of treatment with memantine as monotherapy or bitherapy.

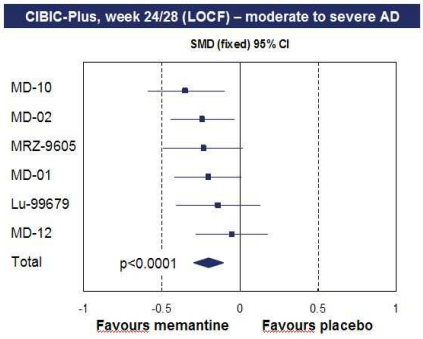
Table 10: Results in LOCF and OC

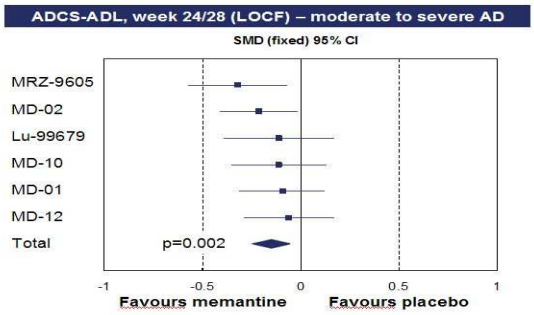
Scale	Standardised effect size[3]	95% CI	Test
LOCF analysis			
ADAS-cog/SIB (cognitive function)	-0.28	[-0.37; -0.18]	<0.0001
CIBIC-plus (global assessment)	-0.20	[-0.30; -0.11]	<0.0001
ADCS-ADL (functional area)	-0.15	[-0.25; -0.06]	0.002
OC analysis			
ADAS-cog/SIB (cognitive function)	-0.26	[-0.37; -0.16]	<0.0001
CIBIC-plus (global assessment)	-0.22	[-0.32; -0.11]	<0.0001
ADCS-ADL (functional area)	-0.18	[-0.28; -0.08]	0.0007

[4] The standardised effect size was assessed using a scale of -1 to 1. A value between -0.3 and -0.5 is considered to be a moderate/average effect of the treatment, while a value between -0.8 and -1 indicates a major effect of the treatment allowing comparisons between areas.

Box 1: Results from the meta-analysis (LOCF)







- Assessment according to the number of patients defined as responders

Table 11: Results of the responders analysis (OC analysis)

MMSE	Placebo	Memantine	Difference	p
Pronounced clinical worsening				
≤ 19	**21%**	**11%**	10%	<0.0001
10 to 19	16%	9%	7%	0.0001
15 to 19	14%	5%	9%	0.0003
Clinical worsening				
≤ 19	**28%**	**18%**	10%	<0.0001
10 to 19	25%	16%	9%	0.0001
15 to 19	22%	12%	10%	0.0026

In conclusion, this meta-analysis of 6 clinical studies lasting 6 months carried out on patients at a moderate to severe stage of the disease (MMSE score < 20) showed a statistically significant effect of memantine compared to placebo in the cognitive, global and functional areas. In patients for whom concomitant worsening in the three areas was identified, the results showed a statistically significant effect on the prevention of a decline, as twice as many patients treated with placebo showed a worsening in these three areas compared to those patients treated with memantine (21% versus 11%, p <0.0001). These results helped to justify extending the indication to moderate forms of the disease.

3.1.5. Results from the Cochrane meta-analysis

Update date: February 22, 2006

Objective: to evaluate the efficacy and safety of memantine in patients with Alzheimer's disease, vascular dementia or mixed dementia, irrespective of the stage of the disease.

Endpoints
The efficacy endpoints were the global assessment, the assessment of cognitive functions and the functional assessment of activities of daily living, neuropsychiatric disorders, trial withdrawals and adverse events.

Studies selected
The effect of memantine in patients with mild to moderate Alzheimer's disease was evaluated based on the studies MD-10, 99679 and MD-12 (described above).
The statistical analyses were carried out on the ITT population using the LOCF method.

Results in patients with mild to moderate Alzheimer's disease after 6 months of treatment with a 20 mg daily dose of memantine or placebo.

Results in favour of memantine
- The global assessment was carried out on a group of 1,281 patients. At the end of the 6-month period of treatment a significant difference was highlighted in favour of memantine based on the CIBIC-plus score (scale between 0 and 7): 0.13 points, 95%CI [0.01; 0.25], p=0.03.

- The assessment of the cognitive functions measured according to the ADAS-cog score (scale between 0 and 70) was carried out on a group of 1,279 patients. At the end of the 6-month period of treatment, a significant difference was observed in favour of memantine: 0.99 points, 95%CI [0.21; 1.78], and p=0.01.

- No significant difference was observed on the rate of withdrawal from the trial between the two groups. The table below shows the number of patients who withdrew from the clinical studies by treatment group.

Table 12: trial withdrawal

Trial withdrawals	Placebo (n, %)	Memantine (n, %)
Patients who withdrew from the clinical studies	106/736 (14.4%)	74/570 (13.0%)
OR	1.16	
95%CI	[0.83; 1.60]	
P	0.38	

Results against memantine
The functional assessment of activities of daily living measured according to ADCS-ADL23 was carried out on a group of 1,271 patients and did not highlight any significant difference in memantine's favour.

The assessment of neuropsychiatric disorders carried out on a group of 1,252 patients, based on the NPI scale, did not highlight any significant difference in favour of the patients treated with memantine: difference of -0.25 points, 95%CI [-1.48; 0.98], p=0.69.

Occurrence of adverse events
- No significant difference was observed between the two groups on the number of patients presenting with at least one adverse event.
- No difference was observed in the number of patients with agitation, but a higher level of drowsiness was highlighted in study MD-10 (p=0.008).

Conclusion

The authors of this meta-analysis concluded that memantine had a marginal clinical benefit with regard to the progression of cognitive disorders after 6 months of treatment in patients starting treatment at a mild to moderate stage (0.99 points on the 70-point ADAS-cog scale CI_{95}: 0.21 to 1.78, p = 0.01). This effect was detected on the CIBIC scale (0.28 points on a 28-point scale), but did not have an impact on the behaviour of the patients evaluated and on the functional evaluation of their activities of daily living. Furthermore, according to the OC analysis, no significant effect on cognition was observed.

Around 2% of patients who took memantine tended to be less likely to become agitated compared to those with placebo (p = 0.04). This effect was small (and observed in particular in patients at a moderately severe or severe stage - cf. Cochrane meta-analysis at this stage of severity). No effect was highlighted in patients already agitated.
Memantine was well tolerated.

The authors of the meta-analysis do not recommend the prescription of memantine for patients with a MMSE score > 15, based on these results.

3.2. Adverse events

The safety data for memantine in patients receiving monotherapy at a moderate stage comes from two clinical studies MD-10 and 99679 described above and from their extension phases (99819). They refer to a limited number of patients (611 patients), provided 159 of them received memantine during 1 year.

Memantine appeared to be well tolerated in these studies compared to the placebo and the frequency of treatment discontinuations due to adverse events was low (between 5 and 10% on average). No unexpected event was highlighted and globally, the incidence of adverse events seemed lower than that observed in patients treated at a more advanced level of severity (cf. EPAR).

The main adverse events expected with memantine at a daily dosage between 10 and 20 mg are headaches, drowsiness, constipation and vertigo. In moderate forms the incidence of hallucinations was lower in patients with memantine (0.8%) than in those with placebo (2.6%). In severe forms it cannot be excluded that memantine causes or worsens hallucinations (cf. SPC).

It should be noted that the EBIXA SPC makes mention of the necessity of a specific monitoring for patients who have had myocardial infarction, severe heart failure or uncontrolled hypertension.

3.3. Conclusions from memantine clinical data in the treatment of moderate stage of Alzheimer's disease

The efficacy and safety of memantine were evaluated considering the results from three placebo-controlled, randomised clinical studies, two conducted using memantine as monotherapy and one in which it was combined with donepezil. The evaluation was conducted over a treatment period of not more than 6 months.

Memantine was more effective than the placebo on cognition and the global clinical impression in only one of these studies. This effect was confirmed by the Cochrane meta-analysis, but the benefit was qualified as "marginal" on the change in cognitive impairment and global assessment. No impact on patient behaviour or the functional evaluation of their activities of daily living was observed.

The efficacy of memantine appears to be of the same magnitude as that observed with cholinesterase inhibitors.

According to the conclusions of several reports recently compiled (SIGN 2006, NICE 2006 and Cochrane 2006 meta-analyses), the prescription of memantine for patients at this stage of severity of the disease (except during investigational studies) is not recommended.

Conducting a clinical study comparing the efficacy and adverse events of memantine with those of an anticholinesterase inhibitor (donepezil, galantamine, rivastigmine) would have been possible, ethical and useful (cf. scientific discussion of the EMEA report). Particularly since the value of combining memantine with an acetylcholinesterase inhibitor has not been established at this stage of severity, according to the results of study MD-12.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

As part of the extension of indication in the treatment of moderate stage of Alzheimer's disease:

4.1 Actual benefit

Alzheimer's disease is a severe and incapacitating degenerative neurological disease of the central nervous system, with considerable family and social repercussions.

It is defined by the association of dementia syndrome with the existence of specific cerebral lesions when a histological examination is carried out on the brain (neuronal loss, presence of neurofibrillary degeneration and amyloid plaque). The best documented neurochemical deficit is the deficit in the cholinergic system (reduction in the synthesis of acetylcholine and the number of cholinergic neurons), but other systems of neurotransmitters are also involved, particularly monoaminergic and glutamatergic systems.

The dementia syndrome is characterised by a progressive deterioration in cognitive functions: memory, language and attention, visual-spatial functions, executive functions for anticipating, initiating and planning tasks, self-awareness and awareness of their environment, gestural abilities (or praxia) and the ability to recognise human beings and objects (gnosia). These disorders are accompanied by a significant impact on the patient's professional and social activities.

Alzheimer's disease is the main cause of dementia syndromes, accounting for two-thirds of cases.

The disease evolution is most often progressive, involving a deterioration in cognitive disorders, dependence (patient's loss of autonomy) with regard to every act of daily living, as well as behavioural disorders which become more and more difficult for the families to tolerate (wandering, delirium, hallucinations). With other forms of dementia, the progression is generally shorter, less insidious and chronic. The patient autonomy is gradually reduced according to the disease's stage of progression. When patient autonomy loss is complete, they need to be admitted to a specialised institution.

The median for survival of patients with Alzheimer's disease is reduced compared with the general population. It was recently estimated at 5 years (according to report published by OPEPS (Parliamentary Office for the Evaluation of Health Policies), 2005).

Nearly 8 out of 10 patients live at home. The disease burden on close relatives is psychological (sleep disorders, depression), physical (increased mortality of carers) as well as financial.
It is estimated that 70% of partners and 49% of children spend more than 6 hours per day caring for patients (OPEPS, 2005).

This progression lasts on average 5 to 10 years when the disease starts under the age of 70 years and 3 to 4 years when it starts after the age of 80 years.

The diagnosis is mainly clinical (NINCDS-ADRDA criteria, DSM-IV criteria) and is based on criteria highlighting a dysfunction evaluated at the end of a neurological, cognitive and behavioural assessment. When the patient uses the healthcare system and when the doctor feels that a diagnostic assessment is justified, the procedures recommended would be fairly well applied[5].

On the other hand, in the Three-City Study[6], major dysfunctions appeared when patients did not use healthcare services or when they complain of the doctor when the latter does not schedule any diagnostic assessment. The frequency of visiting the doctor falls considerably with age, while the frequency of visiting a specialist plummets after the age of 80 from 55% to 19.7%. Based on these results, 4 patients out of 5 over the age of 80 do not have access to the diagnostic procedures officially recommended either because they do not use the healthcare system or because they are complaining about cognitive disorders without the doctor carrying out a diagnostic assessment. An underdiagnosis is also observed in other countries (Finland, Sweden, UK, Canada, US). This data is corroborated by the "Facing dementia survey", an opinion poll carried out by interview in 6 European countries, involving 618 family carers, 96 patients, 605 GPs, 1,200 members of the general population and 60 policy-makers, initiated by Alzheimer International and PFIZER Laboratories. Overall, it seems that there is very little excessive diagnosis of dementia although one case of dementia out of two is diagnosed and one case out of three only at an early stage. The disease seems to be ignored especially in the population of subjects over the age of 85.

Diagnosis made at a very early stage, i.e. when the disease is not very evident clinically with mild cognitive impairment (MCI), is only an area research. No consensual definition has been reached for this stage and does not require any screening.
On the other hand, there is currently a lack of detection or identification of patients in the early stage when the disease is confirmed (up to an MMS score of 20, where this phase can last 1-3 years).

There is no population register in France or any health safety indicators reliable enough to allow the prevalence and incidence of dementia in France to be determined.
This figure is estimated based on epidemiological studies. There currently seems to be 860,000 people in France with dementia, with 220,000 new cases per year, two-thirds of which are likely to have Alzheimer's disease. Half of these cases occur after the age of 85. There currently seems to be around 335,000 people with severe dementia, with roughly 150,000 new cases of severe dementia every year. It is possible that this data are underestimated in real life. Alzheimer's disease appears more frequently in women than men.

- Memantine acts on the disease symptoms. It does not have any established effect on the disease evolution.

- Alternatives to prescribing memantine
There are alternative pharmacological treatments for moderate to moderately severe forms: cholinesterase inhibitors (donepezil, galantamine and rivastigmine).
There is no alternative drug treatment for severe Alzheimer's disease.

[5] Dartigues JF, et al. Prescription des anticholinestérasiques dans la maladie d'Alzheimer en France en 2000-2001: évaluation du respect des procédures diagnostiques et de suiv. Rev Neurol 2005
[6] The 3C Study group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003;22:316-325.

The prescription of psychotropics (especially antipsychotics or antidepressants) for the treatment of mood and behaviour disorders is justified in some patients.
Prescribing drugs is only one part of the patient management strategy. It does not account for the entire strategy. Other types of non-pharmacological intervention might be helpful to patients (memory workshops, occupational therapy, art therapy etc.). The purpose of these would be to stimulate the patients' remaining faculties in order to improve their quality of life. Their scientific validation is being analysed.

Patient management requires coordination with the social agencies.
Sixty percent of those affected by the disease are currently cared for by their families. "Family caregivers"[4] have a vital role to play in managing patients. They help in particular to provide patients with relief and comfort and to keep them in their normal living environment.

Public health benefit

The public health burden represented by Alzheimer's disease is major, taking into account:
- a high prevalence and incidence, which are also actually increasing
- the impact of this disease on the loss of autonomy and on mortality
- the physical, psychological and financial impact of the disease on patients' relatives.

In the sub-population of patients affected by a moderate form of this disease, the burden is significant.
The improvement in the overall management of Alzheimer's disease constitutes a public health need falling within the scope of public health priorities (Public Health Act, Alzheimer's disease plan 2004-2007).
The available studies show the existence of a marginal benefit in moderate forms of Alzheimer's disease, evaluated based on replacement criteria concerning the progression of cognitive disorders and the global assessment. The correlation of this benefit with public health criteria such as the delay of institutionalization, progression to a further stage of severity, the burden on caregivers or the mortality rate has not been established. Furthermore, no comparison is available between EBIXA and acetylcholinesterase inhibitors. It is therefore difficult to determine its role in the treatment strategy for moderate forms.
There is no element capable of indicating the patients who might benefit from this treatment in moderate forms.
Consequently, EBIXA is not expected to have a public health benefit in this extension of indication.

- The efficacy/safety ratio of memantine is moderate.

- It may be prescribed as first-line or second-line treatment.

In conclusion, in spite of the moderate efficacy/safety ratio of these drugs and taking into account the severity of the disease to be treated and the structuring role of the drug in the overall management of Alzheimer's disease, the Transparency Committee considers that the actual benefit of EBIXA in its extension of indication is substantial.

4.2. Improvement in actual benefit

The improvement in actual benefit of EBIXA in the treatment of Alzheimer's disease at moderate stage is minor (IAB IV) in terms of overall patient management.

[7] From January 2007 family support leave ranging from 3 months to 1 year will be made available to caregivers who work.

4.3. Therapeutic use

Current drugs: donepezil (ARICEPT), galantamine (REMINYL), rivastigmine (EXELON), memantine (EBIXA) have a use in patient management.

As therapeutic tools, they contribute to setting up and implementing the patient's overall management strategy.
The symptomatic effect of these drugs has been demonstrated on same cognitive and non-cognitive symptoms of Alzheimer's disease in the short term (6 months in most studies).
Their ability to slow down the disease progression has not been established. Their ability to reduce or to limit the prescription of psychotropic drugs, especially neuroleptics has not been established.

During clinical studies, approximately one third of patients benefit from treatment with a cholinesterase inhibitor or memantine. However, these patients cannot be identified and there is no consensus about how to define the therapeutic response.

Few studies have compared the different drug treatment strategies deployed and the use of drugs is nowadays largely empirical:
- at the mild, moderate and moderately severe stages of the disease, monotherapy with a cholinesterase inhibitor (donepezil, galantamine or rivastigmine) may be considered as first-line treatment. In case of adverse events, one anticholinesterase may be replaced by another.
At the moderate and moderately severe stages, memantine may provide an alternative to cholinesterase inhibitors in same patients. At the moderate stage of the disease, its efficacy is less well established (cf. analysis of clinical data) than that of cholinesterase inhibitors and its use is debated by the experts. According to several recent health technology assessment reports (SIGN 2006, NICE report, technology appraisal guidance 19, 2006), the use of memantine is not recommended for the treatment of Alzheimer's disease.

- at the severe stage of the disease, only memantine/EBIXA is currently indicated in France. However, according to some experts, to continue a well-tolerated cholinesterase inhibitor may be desirable.

Combining memantine with a cholinesterase inhibitor (bitherapy) may also be discussed, given the expected clinical benefit from bitherapy is slight, given only memantine combined with a 10 mg daily dose of donepezil has been assessed (in a single available study whose extraposability is questionable) and given this combination has not proved to be more effective than monotherapy with donepezil in patients at a mild (memantine off-label) or moderate stage of the disease.

There is no consensus about how and when to discontinue these drugs. According to certain experts, complete discontinuation should only be discussed in the case of adverse effects from the drugs or in patients who have reached a very severe stage of Alzheimer's disease.

<u>Notes</u>
- SIGN report, 2006
Scottish Intercollegiate Guidelines Network (SIGN: Management of patients with dementia - 86). A national clinical guideline) recently considered that based on the controlled, randomised clinical studies examined between 1997 and 2004, it was not able to justify and therefore recommend the use of memantine in the treatment of moderate to severe Alzheimer's disease due to the effect on the cognitive symptoms and the impact on the activities of daily living described as small, considered to be not clinically relevant, uncertain or inadequate (associated symptoms).

- NICE report, technology appraisal guidance 19, 2006
Based on a recent report (November 2006) compiled on a HTA carried out by the National Institute for Clinical Excellence (NICE) on the management of Alzheimer's disease using cholinesterase inhibitors and memantine, the use of memantine in patients with moderately severe (MMSE < 14) to severe (MMSE < 10) Alzheimer's disease is not justified outside investigational studies. NICE considered in particular that the clinical data was currently insufficient to determine the clinical effectiveness of memantine in these patients.

4.4. Target population

The target population of memantine (EBIXA) is defined by patients with moderate Alzheimer's disease.

According to the OPEPS report of July 2005, the prevalence of Alzheimer's disease in France is 856,000 persons over the age of 65, with an estimatation of 160,000 new cases per year.
443,000 persons over the age of 75 would be the prevalence of moderate to severe stages of the disease in France, including approximately 180,000 with moderate forms.

According to the experts, the prescription of memantine at this stage of the disease can only be considered if the use of cholinesterase inhibitors has failed or is not tolerated (experts' opinion). There is no data available on use, making it possible to quantify this sub-population of patients who might benefit from treatment with memantine at a moderate stage of Alzheimer's disease.

4.5. Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance (B/56 and oral solution) and on the list of medicinal products approved for hospital use and various public services (for all pack sizes) in the extension of indication: treatment of patients with **moderate** Alzheimer's disease at the dosage given in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%