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Committee for Medicinal Products for Human Use (CHMP)

Ebixa

(memantine)

Procedure No. EMEA/H/C/000463/P45 029

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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INTRODUCTION

On May 2009, the MAH submitted 13 completed paediatric studies for Ebixa, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Ebixa and that there is no consequential regulatory action.

Memantine was approved for treatment of "moderate to severe Alzheimer's disease (AD)" in the European Union (EU) and in the United States. Memantine acts on the glutamatergic system via modulation of N-methyl-D-aspartate (NMDA) receptor activity. The formulation of Axura and Ebixa are identical.

SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the clinical studies

Memantine is currently marketed as a 10 mg and 20 mg film-coated tablet, and as a 10 mg/g oral drops solution. Memantine is not indicated for use in children. So far, no paediatric formulation is available. Tablet was the pharmaceutical formulation mostly used in the the clinical studies submitted in this application. A memantine HCl peppermint-flavored solution (2 mg/mL) and an intravenous formulation were also administered.

Assessor's comment
There are two marketed pharmaceutical forms, film-coated tablets and oral drops, solution. No paediatric formulation is available. Marketed formulations may be suitable for children provided that dosage recommendations for children were generated, size (tablets) or volume (solution) could be easily administered to the target population and an appropriate measuring device could be available in the case of the oral drops solution. The MAH should comment on this as well as the eventual development of an oral formulation especially suitable for children.

Clinical aspects

1. Introduction

The MAH has submitted the studies related to the paediatric use of memantine. This information is originated from three different sources:

a. Recent sponsor-initiated trials, performed in accordance with GCP in **paediatric patients with Attention-Deficit/Hyperactivity Disorder**. The MAH submitted the study report of the following clinical study

a.1 MEM-MD-24: A Pilot Evaluation of the Safety, Tolerability, Pharmacokinetics, and Efficacy of Memantine in Paediatric Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) Combined Type

b. Published investigator-initiated trials reporting the use of memantine in **children, adolescents and young adults with Pervasive Developmental Disorder (PDD).** Only a short summary of the studies has been provided by the MAH.

b.1 Chez et al, 2004. Memantine experience in children and adolescents with autistic spectrum disorders. Ann Neurol 2004; 56 (8): S109

b.2 Chez et al, 2007. Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. J Child Neurol 2007; 22: 574-579

b.3 Erickson et al, 2007. A retrospective study of memantine in children and adolescents with pervasive developmental disorders. Psychopharmacology (Berl) 2007; 19: 141-147.

b.4 Owey et al, 2006. A prospective, open-label trial of memantine in the treatment of cognitive, behavioural and memory dysfunction in pervasive developmental disorders. J Child Adolesc Psychopharmacology 2006; 16: 517-24.

c. Sponsor-initiated trials performed in the 1980 (prior to the publication of EU-GCP Note for Guidance, 1991) targeted on the use of memantine in **motorfunction abnormalities, mainly spasticity**. The MAH has submitted (extended) synopsis of the studies.

c. 1 MRZ90001-Z006: Use of Akatinol Memantine in spasticity syndrome (1981)

c. 2 MRZ90001-Z011: Therapy of spasticity with memantine. Experiences from a multicentre study (1982)

c. 3 MRZ90001-Z012: Clinical observations and experience with Memantine in the treatment of spastic movement disorders (1983).

c. 4 MRZ90001-Z013: Clinical study of the new antispastic agent Akatinol Memantine (1982)

c. 5 MRZ90001-Z015: Experience with memantine in the treatment of severe spastic and extrapyramidal movement disturbances in combination or following stereotactic surgery (1985)

c. 6 MRZ90001-Z034: Surveillance of the clinical course of severe post-contusion functional psychoses under neuro-psychiatric intensive care treatment (1980)

c. 7 MRZ90001-Z038: Study on the efficacy of peroral memantine in spastic patients (secondary to infantile cerebral lesion)

c. 8 MRZ90001-8607: Efficacy and tolerability of Akatinol Memantine in patients with neurogenic bladder dysfunction due to transverse lesion of the cord (1988)

2. Clinical studies

Attention-Deficit/Hyperactivity Disorder (Study MEM-MD-24)

- **Description**

Safety and Efficacy of Memantine in Attention-Deficit/Hyperactivity Disorder

- **Methods**

- ***Objectives***

The current study was designed to provide a preliminary assessment of the tolerability, safety, pharmacokinetics, and efficacy of memantine in paediatric patients 6 to 12 years of age with the diagnosis of ADHD combined type.

- ***Study design***

Single-center (USA), open-label, dose-finding outpatient study.

- ***Study population /Sample size***

Physically healthy paediatric patients 6 to 12 years of age with the following:

- A diagnosis of ADHD (combined type) according to the DSM-IV-TR and a semi-structured interview (the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Versions [K-SADS-PL]) at Screening
- An unsatisfactory clinical response to current ADHD therapy (if currently taking ADHD medication; washout of all psychoactive medications, prior to the completion of the screening period
- A total score of 24 or greater on the ADHD-IV-RS; a score of ≥ 4 on the Disorder CGI-ADHD-Severity, at Baseline
- Intelligence in the non-mentally retarded range, as measured by a standardized score of ≥ 70 on the Peabody Picture Vocabulary Test, Third Edition (PPVT-III), at Screening

The sample size for this open-label pilot study was not based on statistical considerations, but was deemed adequate to address the objectives of this study.

- ***Treatments***

Memantine HCl (2 mg/mL) peppermint flavoured oral solution was supplied. Patients were treated in two different dose cohorts: Cohort 1 (titrated to a maximum daily memantine dose of 10 mg) and Cohort 2 (titrated to a maximum daily memantine dose of 20 mg) for a period of up to 8 weeks-4 weeks of titration and 4 weeks of maintenance therapy.

- ***Outcomes/endpoints***

Safety Measures: Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, physical examinations, and electrocardiograms (ECGs)

Efficacy Measures:

- ADHD-IV-RS, Parent Version
- CGI-ADHD-S
- Conner's Continuous Performance Test, Second Edition (CCPT II)
- Woodcock-Johnson III (WJ III) Math Fluency Test

Pharmacokinetic parameters were measured. PK analyses were performed and are described in a separate study report not submitted.

- ***Statistical Methods***

Safety: Safety analyses were based on the Safety Population (all patients who were enrolled and who took at least one dose of study medication).

Efficacy: The efficacy analyses were performed using descriptive statistics, based on the ITT Population, defined as all patients in the Safety Population who had at least one post-Baseline assessment of ADHD-IV-RS or CGI-ADHD-S. Descriptive statistics were presented by cohort and overall using the last observation carried forward (LOCF) and the observed cases (OC) approaches. No inferential statistics were performed.

➢ **Results**

- ***Recruitment/ Number analysed***

A total of 16 patients, 8 in each cohort, were enrolled and included in the Safety and ITT populations. Eight (8) of 8 patients in Cohort 1 prematurely discontinued from the study, 7 patients (87.5%) for insufficient therapeutic response and 1 patient for withdrawal of consent. As a result, the protocol was amended to allow the subsequent 8 patients (Cohort 2) to titrate to a maximum memantine dose of 20 mg/d. Seven (7) of 8 (87.5%) patients in Cohort 2 reached a final daily dose of 20 mg/d. Of the 8 patients in Cohort 2, 3 patients (37.5%) discontinued because of insufficient therapeutic response; 1 patient (12.5%) was lost to follow-up.

Table 10.3–1. Demographic and Other Baseline Characteristics: Safety Population

Characteristic	*Cohort 1 (N=8)*	*Cohort 2 (N=8)*	*Total (N=16)*
Age (y), mean ± SD	7.6 ± 1.51	8.6 ± 2.39	8.1 ± 2.00
Sex, n (%)			
Male	3 (37.5)	6 (75.0)	9 (56.3)
Female	5 (62.5)	2 (25.0)	7 (43.8)
Race, n (%)			
Caucasian	4 (50.0)	6 (75.0)	10 (62.5)
Black	4 (50.0)	2 (25.0)	6 (37.5)
Asian	0	0	0
Other	0	0	0
Weight (lbs), mean ± SD	62.31 ± 16.57	70.29 ± 24.43	66.30 ± 20.58
Height (in.), mean ± SD	50.91 ± 4.50	52.38 ± 6.62	51.64 ± 5.52
ADHD-IV-RS, mean ± SD	44.6. ± 7.5	41.9 ± 4.6	43.3 ± 6.2
CGI-ADHD-S, mean ± SD	4.6 ± 0.5	4.5 ± 0.5	4.6 ± 0.5

SD = standard deviation.

- ***Efficacy results***

Patient scores on both the ADHD-IV-RS and the CGI-ADHD-S improved relative to Baseline, the largest improvement being observed in the 20-mg/d cohort. No improvement was observed using the cognitive measures CCPT-II, WJ III Math and Reading Fluency tests, and the Stroop Test.

Table 11.1.1–1. Change From Baseline to Week 8 in ADHD–IV–RS Total Score: ITT Population

	Cohort 1 (N=8)			*Cohort 2 (N=8)*		
Time Point	*n*	*Actual Scores Mean ± (SD)*	*Change from BL Mean ± (SD)*	*n*	*Actual Scores Mean ± (SD)*	*Change from BL Mean ± (SD)*
Baseline	8	44.6 ± (7.5)	----	8	41.9 ± (4.6)	----
Week 8 (LOCF)	8	40.9 ± (8.5)	-3.8 ± (2.3)	8	32.9 ± (12.8)	-9.0 ± (10.0)
Week 8 (OC)	----	----	----	4	22.3 ± (8.7)	-16.5 ± (8.2)

BL = Baseline
SD = standard deviation

Table 11.1.1–2. Baseline and Week 8 Total Score in CGI-ADHD-S Score: ITT Population

	Cohort 1 (N=8)		*Cohort 2 (N=8)*	
Time Point	*n*	*Mean ± (SD)*	*n*	*Mean ± (SD)*
Baseline	8	4.6 ± (0.5)	8	4.5 ± (0.5)
Week 8 (LOCF)	8	4.3 ± (0.7)	8	3.3 ± (1.0)
Week 8 (OC)	----	----	4	2.8 ± (1.0)

BL = Baseline

SD = standard deviation

- ***Safety results***

There were no deaths, serious adverse events (SAEs), or AEs that resulted in treatment discontinuation during this study. TEAEs were reported in 4 of 8 (50%) patients in Cohort 1 and 6 of 8 (75%) patients in Cohort 2. TEAEs that occurred in at least three patients and were more common in patients in Cohort 2 compared to Cohort 1 were dizziness, headache, and pyrexia. Most TEAEs occurred during the 4-week titration phase of the study. Most TEAEs were considered mild in severity and not related to study drug. During the study no clinically relevant changes were detected in vital signs, laboratory tests, ECGs, or physical examinations.

Assessor's comment
The use of memantine in ADHD patients was based on preliminary data suggesting that glutamate and NMDA receptor activity may play a role in the pathophysiology of ADHD. Other uncompetitive NMDA receptor antagonist, amantadine has demonstrated activity in children with several different behavioural disturbances.

The interpretation of the results of this pilot study is limited given the open-label design and its small sample size. In principle no dose finding strategy in children appears to be developed. Daily doses of 10 mg/d (half that the dose-approved adult dosage) were initially chosen. This dose showed to be inefficacious in the moderate ADHD population involved in the trial. The results in patients treated with 20 mg/d dosage do not seem neither uncourageous as almost 40% discontinued the study due to lack of efficacy. No safety concerns were identified.

Pharmacokinetic results have not been provided.

2.2 Pervasive developmental disorders (PDD)

A total of 4 investigator-initiated clinical trials were published that reported the use of memantine in children, adolescents and young adults with PDD.

➢ Methods

Table.- Overview on published investigator-initiated studies

Author/ Investigator	**Chez et al, 2004**	**Chez et al, 2007**	**Erickson et al, 2007**	**Owley et al, 2006**
Design	Open, uncontrolled	Open, uncontrolled, add-on to AED (52%), SSRI (32%), psychostimulants (28%)	Retrospective review of patients charts	Prospective, open - label
Indication	PDD Acc. to DSM-IV	PDD Acc. to DSM-IV	PDD Acc. to DSM-IV	PDD Acc. to DSM-IV
No patients (♂:♀) - evaluable	N = 30 (24:6) N= 30	N = 151 (129: 22) N = 105 autism	N = 18 (15: 3) N = 13 (autism)	N = 14 (14:0) N = 10 autism

		N = 46 PDD NOS	N = 2 PDD NOS	N = 2 PDD NOS
Mean range [yrs] (range)	8.92 (UNK)	9.31 ± 4.16 (2.6-26.3)	11.4 ± 3.3 (6-19)	7.8 ± 1.8 (3-12)
Uptitration	UNK	γ	γ	γ
Mode of administration	PO	PO	PO	PO
Average dose (mg/d) (range)	8.1 (2.5-10)	12.67 ± 6.52 (2.5-30)	10.1 ± 6.3 (2.5-20)	0.4 mg/kg (plan: 5-20)
Duration of treatment (range)	18 weeks (8-40)	9.27 ± 4.18 months (1-20)	19.3 ± 19.6 weeks (1.5-56)	UNK (plan 8 weeks)

- **Results**

Table.- Overview on published studies results

Author/ Investigator	Efficacy Outcomes	Efficacy Results	Safety results
Chez et al, 2004	Not standardised scale for improvement in language and behaviour	26/30 patients improved (attention, speech expression, perseveration) N=16 "mod to significant" N=10 "mild to moderate"	No relevant side effects
Chez et al, 2007	CGI-I scale	Language and social interaction: 70.0% "very much improved" 70.7%"much improved" Stereotypic behaviour: 12.1% significant improvement	27 (17.9%) patients prematurely discontinued; 22 because of side effects (mainly worsened behaviour) and 5 because of lack of efficacy.
Erickson et al, 2007	CGI-I scale	61% (11/18) treatment responders (very much or much improved) Predominantly seen for the domains social withdrawal, inattention, language impairment.	AEs in 7/8 patients (39%): increased irritability (n=4), rash (n=1), emesis and sedation (n=1), increased
Owley et al, 2006	CGI-I scale ABC	No significant improvements Improvement on a number of ABC subscales (hyperactivity, lethargy, irritability)	Hiperactivity reported in 5 children (36%)

Assessor's comment
Methodological limitations such as uncontrolled design, retrospective analysis, small sample size, or concomitant treatment with other medication make difficult to draw sound conclusions on the use of memantine in autistic spectrum conditions. Regarding the safety data, up to 40% of the patients enrolled in the clinical studies reported AEs (mainly related to behavioural events).
Apparently initial pharmacokinetic in children will be provided by one study conducted in patients with autistic spectrum disorder (MEM-PK-21). No information has been submitted by the MAH on this issue.

Motorfunction abnormalities (spasticity)

- **Description**

In the 1980ies, a total of 8 clinical studies of phase II have been performed by the MAH. Target indications for the use of memantine were motor function abnormalities, mainly spasticity. For all these trials, only summary information in the form of summary reports and statements is available.

- **Methods**

With one exception all trials were using open and uncontrolled designs. Memantine was often used as add-on therapy to other surgical and/or pharmacological treatment modalities.

Overall the number of patients enrolled in these trials was limited. With one exception (Z038) none of the studies assessed an exclusive paediatric population. The patients enrolled in these trials had a broad age range (from 1 month to 75 years) and in the majority of studies a few paediatric patients only were investigated together with a predominant adult population. Patient groups in these trials were very heterogeneous with regard to underlying pathology, as well as disease duration at the time of treatment initiation. The results cannot selectively be assessed for a paediatric subpopulation.

Table.- Overview on sponsor-initiated trials performed in the 1980s

Author **Year** **Study code**	**Design** **Clinical phase**	**Indication**	**No. patients (♂:♀)** **Mean Age (range)** **Children < 16**	**Target/max dose** **Duration treatm**
Brittinger & Braun **1980** **MRZ 90001-Z006**	Open, uncontrolled Phase II	Central & spinal spasticity IPC and traumatic origin	N = 19 (14:5) UNK (16-23) No (young adults)	30 / 60 mg/d From 1 wk to 4 mth
Ott et al **1983** **MRZ 90001-Z011**	Open, uncontrolled Phase II	Central & spinal spasticity Mainly IPC	N = 97 (57:40) 36.7 (8-75) Yes, few	20/80 8 wks on average
Ott **1983** **MRZ 90001-Z012**	Open, uncontrolled Phase II	Central & spinal spasticity Mainly IPC	N =17 (UNK) 23 (8-61) Yes, few	30 / 30 6 wks–several mths
Rohde **1982** **MRZ 90001-Z013**	Open, uncontrolled Phase II	Central & spinal spasticity Mainly IPC	N = 30 UNK (4-44) Yes, many	< 14 y: 10-20 > 14 y: 30/80 4-14 mth
Mundinger & Milios **1985** **MRZ 90001-Z015**	Open, uncontrolled Phase II	Central & spinal spasticity IPC and traumatic origin	N = 37 (24: 13) 36.2 (9-71) Yes, several	30-60/60 8.2 wks on average
Blaha & Oppolzer **1980** **MRZ 90001-Z034**	Open, uncontrolled Phase II	Posttraumatic brain contusion assoc. with prolonged unconsciousn.	N = 7 (4:3) 21 (14-43) Yes, few	20/20 7 d
Ott **1983** **MRZ 90001-Z038**	Randomised, double-blind, placebo-controll	Central & spinal spasticity Mainly IPC	N = 22 (UNK) UNK (4-16) Yes, number UNK	20/ UNK UNK (not fixed)
Dunzendorfer **1988** **MRZ 90001-8607**	Open, uncontrolled Phase II	Traumatic spinal cord lesion focus on neurog bladder dysfunction	n=32. 41 (16 – 73) No	60 mg / UNK 6 weeks

- **Results**

- ***Efficacy results***

Significant post-treatment improvements in spasticity and/or reductions in muscle spasm were reported by investigators in all studies. The percentage of "treatment responders" differed among studies; at least in part this may have been due to the heterogeneous patient groups enrolled (various underlying pathologies and/or treatment start at various intervals after the initial event). Best results were reported in patients with moderate degree of spasticity of limited duration, as in these cases, secondary anatomical changes (i.e. occurrence of progressive joint contractures and limb deformities due to shortening of joint capsules, ligaments and tendons) are less severe.

- ***Safety results***

Only very limited information regarding the safety and tolerability of memantine in a paediatric population can be derived from these trials.

Table.- Overview on published studies results

Author Year Study code	Efficacy outcomes	Efficacy results	Safety results
Brittinger & Braun 1980 MRZ 90001-Z006	Subjective well-being, neurological status, blood pressure, pulse	Subjective improvement of spasticity: Good/very good (n=11); no effect (n=1)	Drop outs: Intolerance phenomena, depression, impaired concentration, restlessness, dizziness, fatigue, exanthema. AEs: Initial depression and impaired concentration(1), initial fatigue (1), intermittent headache (1), occasional nausea (1), and mouth dryness (1). No negative impact on EEG or laboratory values.
Ott et al 1983 MRZ 90001-Z011	Neurological status, phychological findings, somatic findings	"Spasticity" improved in 72% of the patients	AEs: dizziness, drowsiness, impaired concentration, fatigue, diarrhoea, vomiting, headache, aggressiveness, weakness, depression and exanthema.
Ott 1983 MRZ 90001-Z012	Neurological status, time of beginning of the effect, performance features, phychological findings, somatic findings	Marked improvement of motor symptoms (decrease of muscle tone, regression of hyperkinesia) in patients with early brain damage. Limited response in patients with motor dysfunctions of other origin. Impulse-increasing and mood-lifting effects were observed.	Two patients dropped out due to restlessness, one due to intolerability of the drug (not specified). No other safety data available.
Rohde 1982 MRZ 90001-Z013	Assessment by physiotherapist and parents, electromyography.	Spasticity improvement: Good to very good (n=17), slight to moderate (n=10), no effect (n=3)	Increased fatigue (n=5), deterioration of motor control (n=2), acute visual disturbance (n=1). Laboratory values: ↑transaminases and GGT (n=2), elevation of liver values (n=3), enzyme increase within the normal range (n=4), slight thrombopenia (n=2), urea increase (n=1)
Mundinger & Milios 1985 MRZ 90001-Z015	Physical examination, spasticity, assessment of neurological effect, and over-all assessment	In 17 patients marked functional improvement of neurological symptoms (spasticity and dyskinesia). Positive effects on emotional condition (8), articulation in speaking (9), intellectual activity and concentration (7)	Eight patients reported AEs: dizziness, drowsiness or nausea; in one patient, sensation of ocular pressure. Balance impairment and hypotonia in one patient resolved after dose reduction.
Blaha & Oppolzer 1980 MRZ 90001-Z034	Level of consciousness, functional psychosis scale B, EEG, pK	No influence on the level of consciousness in 4 patients, moderate improvement in 1 patient, marked improvement in 2 patients.	Not reported.
Ott 1983 MRZ 90001-Z038	Effects on clinical parameters	Positive effect on muscular spasticity, extrapyramidal motor dysfunction and on the frequency of seizures	NI
Dunzendorfer 1988 MRZ 90001-8607	Global clinical evaluation Urodynamics and bacteriological evaluation	Global efficacy n=27patients Good (2), moderate (11), insufficient (14). ↓ residual urine volume, ↑bladder capacity, ↑pressure of intravesical wall.	AEs in 24 patients. Loss of appetite, sweating increased, gastric and abdominal pain, vomiting, dry mouth, agitation and restlessness. M More rarely: orthostatic hypotension, hypersalivation, accommodation disturbance, dizziness and confusion

Assessor's comment
The MAH has provided short reports of 8 clinical studies conducted under non-GCP conditions. Most of them show relevant methodological limitations (uncontrolled design, small sample size, few paediatric patients in some of the studies, short duration of treatment). Both efficacy and safety results appear of insufficient quality to draw any conclusion about the use of memantine in the treatment of spasticity in paediatric population.

Rapporteur's Overall Conclusion AND RECOMMENDATION

- **Overall conclusion**

The MAH has submitted information about the available results from the clinical investigation in paediatric population. This investigation involves three areas: Attention-Deficit/Hyperactivity, motor function abnormalities and autistic spectrum disorder. These indications are not approved in adults or elderly patients. Efficacy and safety results coming from the submitted studies conducted in the paediatric population are inconclusive. The benefit/risk of the product does not require to be updated in this respect.

Some information about pharmacokinetic characterisation in children and adolescent subjects seem to be generated by different pharmacokinetic studies (or analyses). These data have not been submitted in this variation. Once these data are received, it should be assessed whether the information provided is sufficiently robust to update the SPC accordingly. Therefore, the MAH is asked to provide and discuss it.

- **Recommendation**

x Not fulfilled:
Based on the data submitted, the MAH should provide clarification about the development of a paediatric formulation and pharmacokinetic characterisation in children and adolescents as part of this procedure Ebixa P45 (see section IV "Additional clarifications requested")

ADDITIONAL CLARIFICATIONS REQUESTED

Based on the data submitted, the MAH is requested to submit their responses to the two questions below within 1 month. The responses will be assessed as follow-up measure P45.1.

1. The MAH should comment on the suitability of the marketed formulations for children as well as the eventual development of an oral formulation especially suitable for this population.

2. Some information about pharmacokinetic characterisation in children and adolescent subjects seem to have be generated in different PK studies (or analyses). These data have not been submitted in this procedure. The MAH is therefore asked to provide the data and to further discuss them.