EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2012
EMA/111381/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Acrescent

International non-proprietary name: **memantine hydrochloride / donepezil hydrochloride**

Procedure No. **EMEA/H/C/002424**

Note

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

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List of abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAG-cog	Alzheimer's disease assessment scale – cognitive subscale
ADCS-ADL	Alzheimer's disease cooperative study – activities of daily living inventory
ADCS-CGIC	Alzheimer's disease cooperative study – clinical global impression of change
ADDF	Alzheimer's drug discovery foundation
ADL	Activities of daily living inventory
ADMC	Alzheimer's Disease Management Council Clinical Consensus Panel
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ANCOVA	Analysis of covariance
APTS	All patients treated set
ARW-DSP	Adelphi Real World Disease Specific Programme
ASHA-FACS	American speech-language-hearing association functional assessment of communication skills for adults
AUC (0-24h)	Area under the plasma concentration-time curve from zero to 24 hours post-dose
AUC(I)	Area under the % inhibition-time curve
BALDS	Bristol Activities of Daily Living Scale
BBSI	Brain boundary shift integral
BCS	Biopharmaceutics classification system
BDS	Blessed Dementia Scale
BGP	behavioral rating scale for geriatric patients
BMI	body mass index
BuChE	Butylcholinesterase
CCI-OT	Cegedim Customer Information Online Tracker
CGI-I	Clinical global impression – global improvement
CGI-S	Clinical global impression – severity of illness
CI	Confidence interval
CIBIC	Clinician's interview-based impression of change
Cl/F	Oral clearance; defined as dose/AUC0-inf
Cltot	Clearance total
CMAI	Cohen mansfield agitation inventory
Cmax	Maximum plasma concentration
CSD-LPD	Cegedim strategic data- longitudinal patient databases
CSF	Cerebro spinal fluid
CT	Computerised tomography
DE	Germany
EFNS	European Federation of Neurological Societies
ERA	Environmental risk assessment
ER	Extended release formulation
ES	Spain
EU	European Union
FAS	Full analysis set
FAST	Functional assessment staging
FDC	Fixed dose combination
FLCI	Functional linguistic communication inventory
Fpen	Fraction of a population receiving the drug substance during a given time
FR	France
GCP	Good clinical practices
GLP	Good laboratory practices
GP	General Practitioner
HIS	hachinski ischaemia scale
HSQ-12	health status questionnaire
IC	Half maximum inhibitory concentration
Imax	Maximum percentage of inhibition

IMP	Investigational medicinal product
IMS-IPD	IMS-Prescribing Insights Database
ip	intraperitoneal
IT	Italy
ITT	Intent to treat
LC/MS/MS	Liquid chromatography with tandem mass spectrometric detection
LOCF	Last observation carried forward
Log Kow	octanol-water partition coefficient
MADRS	Montgomery and åsberg depression rating scale
MCID	Minimal clinically important difference
MDS	Minimum data set
MEM/DPZ	Memantine/ donepezil
MMSE	Mini mental state examination
MoA	Mechanism of Action
MOSES	Multidimensional Observation Scale for Elderly Subjects
MRI	Magnetic resonance imaging
NICE	National institute for health and clinical excellence
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse effect level
NPI	Neuropsychiatric inventory
NPI-NH	Neuropsychiatric inventory- nursing home
OC	Observed Case
PANSS-EC	positive and negative syndrome scale – excited component
PBO/DPZ	Placebo/ donepezil
PECsw	Estimation of exposure of surface water (for calculation)
pKa	Acid dissociation constant
RBC	Red blood cell
RUD	Resource utilization in dementia
SAE	Serious adverse event
SIB	Severe impairment battery
SMMSE	Standardised mini-mental state examination
TBV	Total brain volume
TK	Toxicokinetic
Tmax	Time to maximum observed concentration
UK	United kingdom
US	United states
Vz/F	Apparent volume of distribution; calculated as cl/f/λz

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant H. Lundbeck A/S submitted on 1 June 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Acrescent, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 September 2010. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication: treatment of patients with moderate to moderately severe Alzheimer's disease who are already on a stable daily dose of 20 mg memantine and 10 mg donepezil.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – new fixed combination application.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Concepcion Prieto Yerro**

Co-Rapporteur: **Bruno Sepodes**

- The application was received by the EMA on 1 June 2011.
- The procedure started on 22 June 2011. The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 September 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 September 2011.
- During the meeting on 20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 May 2012.
- During the CHMP meeting on 24 May 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues on 3 September 2012.
- During the CHMP meeting on 18 September 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

During the meeting on 18 October 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion.

2. Scientific discussion

2.1. Introduction

This is a fixed combination application, Article 10(b) application for Acrescent (Memantine/Donepezil) for known active substances through the centralised procedure. The fixed combination product is intended for prescription only.

Memantine is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. It is claimed as a modulator of the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction and has been authorised via the centralised procedure for the treatment of patients with moderate to severe Alzheimer's disease (AD).

Donepezil is a selective, reversible acetylcholine esterase inhibitor (AChEI), the predominant cholinesterase in the brain. Donepezil has been authorised via the mutual recognition procedure in several Member States for the symptomatic treatment of patients with mild to moderately severe Alzheimer´s dementia.

AD is a slowly progressive disease of the brain that is characterized by impairment of patient's cognition and eventually by disturbances in reasoning, planning, language, and perception. AD results from an increase in the production or accumulation of beta-amyloid protein and degeneration of neurons. As the disease progresses, the neurodegeneration spreads and affects also serotonergic, noradrenergic, and glutamatergic neurons. The incidence of Alzheimer's disease is approximately 10% in the population over 65 years of age and increases progressively with age to reach about 30% by the end of a century of life. Currently, available pharmacological therapies are the AChEI (e.g donepezil, galantamine and rivastigmine) and memantine that are acting on AD with different mechanisms of action (MoA) as explained above.

Acrescent is a fixed-dose combination (FDC) product of memantine (20 mg) and donepezil (10 mg), presented as film-coated tablets (memantine 20 mg/donepezil 10 mg). Acrescent has been developed as a substitution indication i.e. in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets. This simplification of therapy by decreasing the number of individual dose units to be taken by the patient may improve patient compliance and was therefore considered as a potential therapeutic advantage to support the present application.

The claimed indication is: treatment of adult patients with moderate to moderately severe AD who are already on a stable daily dose of 20 mg memantine and 10 mg donepezil. The recommended dose is one tablet per day.

2.2. Quality aspects

2.2.1. Introduction

Acrescent is a fixed dose combination product of two well-known stable active substances, memantine hydrochloride and donepezil hydrochloride. It is presented as film-coated tablets containing 20 mg memantine/10 mg donepezil in alu/alu blisters.

The full list of ingredients is defined in section 6.1 of the SmPC.

2.2.2. Active Substance

Memantine hydrochloride

Memantine chemical name (IUPAC) is 3,5-dimethyladamantan-1-amine hydrochloride . It appears as is a white, almost odourless crystalline powder, highly soluble in water. Its pKa-value is 10.3 and shows a partition coefficient of log P = 3.28. The active substance has two chiral centres but since there is a plane of symmetry between them, the molecule is not chiral and it exhibits only one polymorphic form.

It corresponds to the molecular formula C12H21N•HCl and has a molecular mass 215.77 g/mol (as hydrochloride); 179.31 g/mol (free base).

Manufacture

The active substance memantine hydrochloride is sourced from two different sources. One of the suppliers utilizes two different synthetic routes. The documentation on the active substance is presented in three different Active Substance Master Files (ASMF). The synthetic steps are described in all three ASMF sufficiently. Details regarding the materials, intermediates, process validation and manufacturing process development have been satisfactorily presented. The synthetic processes used by the proposed manufacturers are very similar. The starting material used in the synthesis of Memantine HCl is the same for the three processes. The same intermediates are obtained, but they could be isolated or not depending on the process. Moreover, there are small differences in a solvent, some reagents and reaction conditions among the processes, but these differences are of no relevance, since they are consequence of optimization of the process in the respective manufacturing facilities.

Specification

The specification of the memantine as set up by the drug product manufacturer includes tests and limits for appearance, colour and colour of solution (visual), odour (organoleptic), solubility (visual), identification of active substance and chloride (IR, chemical), assay of active substance and chloride (titration), impurities (GC or HPLC), heavy metals (Ph. Eur.), residual solvents (GC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.) and particle size (laser diffraction). Satisfactory justification has been presented for the omission of microbiological testing in the specification of memantine. Sufficient justification on the proposed controls has been provided in accordance with the Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006) for the potential genotoxic impurities.

The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data is presented for at least three production batches manufactured by all three processes from each memantine supplier. All the results reported are all within the proposed specifications.

Stability

The stability studies were carried out on at least three commercial scale batches of memantine hydrochloride from both suppliers manufactured by all proposed processes.

Results were presented for up to 60 months at 25ºC/60%RH and 6 months at 40ºC/75%HR according to defined stability protocols, and in accordance with the ICH guidelines on stability. Memantine was packaged in all cases in the simulate market container.

The stability samples were evaluated as per defined stability protocols for appearance, water or loss on drying, assay, and impurities. Depending on the stability protocol some samples were also tested for identification, clarity of solution, colour of solution.

The test methods used during stability are those used for release. The analytical methods used have been suitably validated and are stability indicating methods.

Photostability and stress testing (acidic and alkaline hydrolytic and oxidative) of the active substance has been investigated on two representative batches of the active substance and no significant degradation has been observed when exposed to light or other stress tested conditions apart from oxidative treatment with KMnO4.

The proposed re-test period and storage conditions are supported by the overall results.

2.2.3. Active Substance

Donepezil hydrochloride

Donepezil chemical name chemical name (IUPAC) is 2-[(1-benzyl-4-piperidyl)methyl]- 5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride monohydrate. It appears as is a white to off-white, slightly hygroscopic crystalline powder, freely soluble in water, methanol and acetic acid. Its pKa-value is 9.08. It corresponds to the molecular formula C24H29NO3•HCl•H2O and has a molecular mass 433.98 g/mol (as hydrochloride hydrate); 379.50 g/mol (free base). It has one chiral centre and the active substance is a racemic mixture.

It exhibits polymorphism and exists in different polymorphic forms designated form I, II, III, IV and V. Donepezil hydrochloride synthesised by both suppliers is the same form I, based on the comparison of IR spectra and X ray powder diffraction patterns.

Manufacture

The active substance donepezil hydrochloride is sourced from two different sources. The documentation on the active substance Donepezil hydrochloride is also presented as two separate ASMFs. The synthetic steps are described in both ASMFs sufficiently. Details regarding the materials, intermediates, process validation and manufacturing process development have been satisfactorily presented. The synthetic processes used by the proposed manufacturers are very similar. Some differences in solvents, reagents or reaction conditions are minor and both processes yield material of comparable quality.

Specification

The specification of donepezil as set up by the drug product manufacturer includes tests and limits for appearance (visual), identification of active substance and chloride (IR, HPLC, chloride: Ph. Eur.), assay (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), residual solvents (GC), water (Ph. Eur.), microbiological purity (Ph. Eur.- not routinely), and sulphated ash (Ph. Eur.).

Sufficient justification on the proposed controls and limits has been provided in accordance with the Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006) for the potential genotoxic impurities.

The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data is presented for at least three production batches from each donepezil supplier. All the results reported are all within the proposed specifications.

Stability

The stability studies results were presented on six commercial scale batches of donepezil manufactured the one supplier and on three commercial scale batches from the second

Results were presented for up to 36 months at 25ºC/60%RH and 6 months at 40ºC/75%HR according to defined stability protocols, and in accordance with the ICH guidelines on stability. Donepezil was packaged in both cases in the simulate market container.

The stability samples were evaluated for appearance, assay, water, related substances and identification. The test methods used during stability are those used for release. The analytical methods used for determination of assay and related substances have been suitably validated as stability indicating methods.

Photostability of the active substance has been investigated by both suppliers as per the relevant ICH guideline. No significant degradation has been observed when exposed to light.

Stress testing hydrolytic and oxidative conditions in solution and in powder form has been performed. The structures of probable degradation products in hydrolytic and oxidative conditions have been provided and are considered not to raise any concern.

The proposed re-test period and storage conditions are supported by the overall results.

2.2.4. Finished Medicinal Product

Pharmaceutical Development

Acrescent fixed dose combination formulation was designed as film tablet to be bioequivalent to the marketed 20 mg memantine hydrochloride tablets Axura / Ebixa and 10 mg donepezil hydrochloride tablets Aricept.

Acrescent finished product is presented as pale yellow to light yellow, oval shaped film-coated tablet with imprint “MEM” on one side and imprint “DON” on the other side.

The starting point for the formulation development activities was the existing and successfully marketed drug products Axura / Ebixa 20 mg film coated tablet and their established and validated manufacturing process.

Both active ingredients, memantine hydrochloride and donepezil hydrochloride monohydrate, are crystalline powders with suitable flow properties. The qualitative composition of the marketed drug product Axura / Ebixa 20 mg film coated tablet was in principle not modified apart from the addition of donepezil.

Although it is known that crystalline memantine can exist in two plates and needles, the results provided by the two manufacturers showed consistently the same needle shape. Donepezil exists in various polymorphic forms but only the polymorph 1 is was used in the formulation.

Because the solubility of both active substances is very high and are classified as BCS class I compounds, their particle size is not considered critical in the manufacturing process and the product performance. Both substances are rapidly dissolved from the dosage form (within 15 min).

All excipients in the formulation are standard excipients of pharmaceutical quality appropriate for their intended use and have been used in oral solid dosage forms for already long time.

The compatibility between the actives substances and excipients was demonstrated by stress studies of binary mixtures between the active substances and the excipients.

The manufacturing process is based upon the manufacturing process approved for the marketed memantine 20 mg film-coated tablets. The process parameters have been optimised with regard to the core tablets and the coating. It has been found the process is unaffected by the changes introduced. In-process control tests were identified to control the manufacturing process adequately.

The impact of the different active substance sources was investigated during development and it was found it does not affect manufacture or the finished product quality. Scaling up and the influence of the main manufacturing process operations was investigated and no critical parameters were identified.

The drug product will be packaged in aluminium/aluminium blister pack.

Adventitious agents

The tablets do not contain excipients of human or animal origin.

Manufacture of the product

The manufacturing process is essentially the same as the approved for Axura/ Ebixa tablets. It is a standard direct compression method for tablet manufacture comprising several blendings, compression and film coating. There are no critical steps in this manufacturing process. Data obtained during the development of the proposed product together with extensive experience in the manufacture of Axura/ Ebixa 20 mg tablets demonstrate that the manufacturing process is robust. The in-process controls are considered suitable and sufficient to ensure the quality of the tablets manufactured. There are no intermediates isolated during the manufacture of the tablets.

The process will be validated on the first three consecutive production batches which is acceptable taking into account that is a standard manufacturing process and the experience with very similar authorised products.

Product specification

The finished product release and shelf-life specifications includes tests and limits for appearance (visual), identification (HPLC, UV), assay (HPLC), uniformity of mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.- non routinely), degradation products (GC and HPLC), dissolution (HPLC- Ph. Eur.) and Microbial quality (Ph. Eur.- non routinely).

Satisfactory batch data have been provided for three commercial scale batches. All parameters were within specification. The reported results indicate that the process is under control, confirming consistency and uniformity of manufacture.

Stability of the product

The stability studies were conducted on six pilot batches of tablets at 25°C/60%RH, 30ºC/75%RH and 40°C/75%HR according to defined stability protocols, which follow the ICH guidelines on stability.

The batches were packed in the proposed packaging. Results were presented for up to 18 months at 25ºC/60%RH and 30ºC/75%RH and up to12 months at 40ºC/75%RH.

Samples have been tested for appearance, uniformity of mass and average weight, dissolution, assay, purity and microbiological quality. The parameters are considered relevant and adequate to assess the stability of the drug product. The analytical methods used for determination of assay and related substances have been suitably validated as stability indicating methods.

A slight increase of the content of some donepezil related degradation product at accelerated conditions after 9 months was observed. However they still remain well within the shelf life specification limits. For all other parameters tested no significant changes are observed.

Stability of bulk tablets has been studied and appropriate shelf life and storage conditions have been established

The proposed shelf-life and storage conditions are considered justified.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non clinical programme considered the CHMP Guideline on the Non-Clinical Development of Fixed Medicinal Products (CPMP/SWP/258498/2005) and was limited to two non clinical studies characterising the pharmacodynamic and toxicology profiles of the use of this combination. All other submitted data were derived from the literature.

The pivotal toxicology study was performed according to Good Laboratory Practices (GLP), as stated by the applicant.

2.3.2. Pharmacology

A limited pharmacology program has been conducted by the applicant and consisted of one study specifically evaluating the effect of the combination (memantine/donepezil) on extracellular acetylcholine levels.

2.3.2.1. ***Primary pharmacodynamic studies***

Memantine

Memantine is an uncompetitive NMDA receptor antagonist and was found to have a free brain exposure of 0.5-0.8 µM at clinical relevant doses obtained 30-60 min after 5 mg/kg intraperitoneal (i.p) administration in rats. Memantine also blocked NR1 co-expressed with NR2A, NR2B, NR2C or NR2D receptors in Xenopus oocytes with IC50 of 0.89 µM, 0.40 µM, 0.32 µM or 0.28 µM respectively. Memantine has shown to interact with 5HT3 and nAChR receptors with IC50 values of 2.29 µM and 6.6 µM respectively. On α7 nAChR, the potency of memantine varied considerably from 0.3 µM to 6.6 µM depending on expression system. Memantine also exhibited generalization to other NMDA receptor antagonists, with a modest attenuation to nicotine at 10 mg/kg i.p. in rats, indicative for a predominant NMDA receptor block.

Donepezil

Donepezil is a selective non-competitive piperidine-class AChE inhibitor. Donepezil showed inhibitory effects on rat brain AChE and rat plasma ButylCholinesterase (BuChE), with an IC50 of 6.7 µM and 7.4 µM, respectively. Oral administration of donepezil inhibited brain AChE in a dose-dependent manner. The estimated p.o dose of donepezil to inhibit 50% of brain AChE is 2.6 mg/kg in rats.

2.3.2.2. ***Secondary pharmacodynamic studies***

No studies described specifically as secondary pharmacodynamic have been performed with the combination (memantine/donepezil).

2.3.2.3. ***Safety pharmacology programme***

No safety pharmacology studies have been performed with the combination (memantine/donepezil).

2.3.2.4. ***Pharmacodynamic drug interactions***

The applicant specifically evaluated the effect of the combination (memantine/donepezil) on extracellular acetylcholine (ACh) levels by microdialysis in dorsal hippocampus of freely moving rats. Results showed that 5 mg/kg s.c of memantine did not produce any measurable changes in ACh while 1.3 mg/kg subcutaneous (s.c) administration of donepezil induced a 1223% ± 239% increase in ACh at the maximal effect after 80 minutes. Literature data also reported increases on brain extracellular concentration of ACh (and dopamine and noradrenalin) at high memantine doses (20 mg/kg i.p.). In the presence of neostigmine and memantine (5mg/kg), ACh level was found to be increased of 160% in the tested region (hippocampus). Additional systemic inhibition by donepezil (0.5 mg/kg) increased the ACh level by approximately 600%, in the presence of memantine (5mg/kg).

Based on literature, in vitro data suggested that there was no attenuation of the effect of donepezil inhibition on AChE in the presence of memantine at either 1 µM or 5 µM. Memantine alone at the same doses did not significantly inhibit AChE activity. Ex vivo data also showed an acetylcholinesterase (AChE) inhibition of about 50% and 80% with 0.75 mg/kg and 1.5 mg/kg of donepezil, respectively. Pre-treatment with 10 mg/kg of memantine, i.p dose above the clinical relevant exposure in humans (5 mg/kg), did not change the activity of donepezil in either of two tested regions (hippocampus, cortex), dose well above the clinical relevant exposure in humans (5 mg/kg). The combination of donepezil (50 µM) and NMDA on primary hippocampal neurons showed an elicited response that was about 98% of the response obtained in the absence of donepezil.

2.3.3. Pharmacokinetics

No non clinical studies specifically investigating absorption, distribution, metabolism, elimination (ADME) of the combination (memantine/donepezil) and its drug interaction profile have been performed.

2.3.4. Toxicology

A limited toxicology program has been conducted by the applicant and consisted of one repeated dose toxicology study with the combination (memantine/donepezil) using the oral route. In addition, a single toxicity study was ongoing at the time of submission. At the CHMP request, these data were subsequently provided during the evaluation.

2.3.4.1. ***Single dose toxicity***

Female rats were dosed by oral gavage with 8/0, 30/0, 60/0, 8/5, 60/5, 8/10, 30/10, 60/10, 0/5, or 0/10 mg/kg memantine/donepezil in combination. A vehicle control and a positive control (MK-801, i.p.) were also included. In addition, one group of rats was dosed once by i.p injection (in the right lower abdominal area) with 30/10 mg/kg memantine/donepezil in combination. There were signs of general toxicity that included decreased activity, anogenital staining, and decreased fecal volume, at 30/10 and 60/10 mg/kg memantine/donepezil, and stain on torso fur and chromodacryrrhea for the 60 mg/kg memantine alone group and at 60/5 mg/kg memantine/donepezil. Mortality was observed for 3 females at 30/10 mg/kg memantine/ donepezil given i.p. In addition, one female receiving at 60/0 mg/kg memantine/donepezil was found in a moribund condition and euthanized at day 2. This finding was not considered related to the tested article and may have been caused by injury during a toxicokinetic blood collection from the jugular vein. No degeneration in the brain was seen with donepezil alone (5 and 10 mg/kg) and memantine alone at 8 mg/kg. Higher doses, i.e. 30 and 60 mg/kg memantine alone showed mild effects. Memantine and donepezil in combination at 30/10 mg/kg caused degeneration in the brain that was present in greater numbers of rats as compared to the 30/0 mg/kg group and was considered generally minimal in severity. There was a substantial potentiation of degeneration in the brain at 60/10 mg/kg. The range of affected brain sites was markedly greater in rats administered the 60/10 mg/kg as compared to other treatment regimens with severity grades of mostly moderate to marked.

2.3.4.2. ***Repeat dose toxicity***

A repeated dose toxicity was conducted for 28 days. Female rats were dosed by oral gavage at levels of 0, 3, 10, 30 and 60 mg/kg/day; donepezil at levels of 0, 3 and 10 mg/kg/day; and the combination of memantine/donepezil at levels of 0/0, 3/3, 10/3, 30/3, 60/3, 0/0, 3/10, 10/10, 30/10 and 60/10 mg/kg/day, according to a specified time schedule. A vehicle control and a positive control (MK-801, i.p.) were also included.

Mortality occurred during the first eight days of dosing. Unscheduled deaths were observed in 1, 1, and 3 rats in the 60/0, 30/3 and 60/10 mg/kg/day memantine/donepezil combination dosage groups, respectively. Necropsy findings for these premature decedents were unremarkable and a lack of test article relationship could not be established. In addition, 2, 2, 1, 4, 1 and 1 animals in the 60/0, 30/3, 30/10, 60/10, 0/3 and 0/10 mg/kg/day memantine/ donepezil combination toxicokinetic (TK) groups were found dead and the cause of death was not determined. Four other unscheduled deaths (1, 2, and 1 rats in the 30/0, 3/3 and 10/3 mg/kg/day memantine/donepezil combination groups,

respectively) occurred during the study. These animals had necropsy findings compatible with a gavage accident. One animal was sacrificed for human reasons after accidental injury.

Stained fur (anogenital stains, or otherwise), excessive salivation, lacrimation, tremors, decreased activity and/or chromodacryorrhea were observed in the 60/10 mg/kg/day memantine/donepezil combination group. These clinical signs were also observed, but for a lesser number of days, in the groups receiving 60/3 and 30/10 mg/kg/day of the memantine/ donepezil combination. In the groups given memantine alone, stained fur and chromodacryorrhea occurred in two animals in the 60 mg/kg/day group for a number of days, and infrequently at 30 mg/kg/day. Lacrimation and excessive salivation was recorded infrequently at doses ≥ 30 mg/kg/day.

One, 1, 1 and 2 rats in the 60/0, 60/3, 30/10 and 60/10 mg/kg/day memantine/donepezil combination groups, respectively, had neurodegenerative lesions in one or more regions of the brain. All animals evaluated in the 0.5 and 3 mg/kg dosage groups of MK-801, the positive control, had neurodegeneration in one or more regions of the brain.

Toxicokinetic data collected from this study showed a dose-dependent increase in exposure as memantine dose increased. Increases in memantine maximum plasma concentration ($C_{max)}$ were relatively dose proportional as memantine dose increased while increases in area under the plasma concentration-time curve from zero to 24 hours post-dose (AUC_{0-24}) were generally greater than dose proportional. There was some accumulation of memantine by day 28, most notably at 30 and 60 mg/kg/day where C_{max} and AUC_{0-24} increases were 2-fold greater than the corresponding day 1. Time to maximum observed concentration (T_{max}) was generally between 0.5 and 2 hours and 1 and 4 hours on days 1 and 28, respectively. Mean apparent elimination half life (t½) increased as memantine dose increased, ranging between 3 and 9 hours and 3 and 5 hours on days 1 and 28, respectively. Donepezil exposure was variable with fixed donepezil doses and varying memantine doses, with no clear pattern of exposure increases or decreases correlating with increasing or decreasing memantine doses. Dose-dependent increases in exposure were observed as donepezil dose increased. Dose proportionality with donepezil exposure was generally observed with C_{max} and AUC_{0-24} on days 1 and 28. There was no apparent accumulation of donepezil by day 28 at 3 mg/kg/day, however, a slight increase in AUC_{0-24} was observed on day 28 at 10 mg/kg/day. T_{max} was about 0.5- 2 hours at 3 mg/kg/day and 0.5-4 hours at 30 mg/kg/day. T½ was greater on day 1 at both donepezil doses, regardless of memantine dose, than on day 28.

2.3.4.3. ***Genotoxicity***

No genotoxicity studies have been performed with the combination (memantine/donepezil).

2.3.4.4. ***Carcinogenicity***

No carcinogenicity studies have been performed with the combination (memantine/donepezil).

2.3.4.5. ***Reproduction Toxicity***

No reproduction toxicity studies have been performed with the combination (memantine/donepezil).

2.3.4.6. ***Toxicokinetic data***

Toxicokinetic data are addressed in the repeated dose toxicity study (see above).

2.3.4.7. ***Local Tolerance***

Single and repeated dose toxicity studies with the combination (memantine/donepezil) addressed local tolerance. No relevant findings were observed.

2.3.4.8. ***Other toxicity studies***

No other toxicity studies have been performed with the combination (memantine/donepezil). No relevant findings were observed regarding potential for antigenicity and immunotoxicity in the repeated dose toxicity study with the combination (memantine/donepezil).

2.3.5. Ecotoxicity / environmental risk assessment

No formal environmental risk assessment (ERA) has been conducted for the combination (memantine/donepezil), in accordance to the EMEA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). According to the applicant, Log Kow value were respectively 3.28 for memantine and 2.3 for donepezil at pH=7.4. The PECsw for memantine and donepezil, using a refined Fpen, were 0.0020 µg/L and 0.0010 µg/L, respectively, and, since both values were below the threshold value (0.01 µg /L), the applicant concluded that a phase II assessment was not required.

However, having considered the data submitted in the application, the CHMP did not conclude on whether or not the combination could pose a risk for the environment at this time for the following reasons:

- The calculations used to determine the pKa of donepezil were not fully provided by the applicant to accept its Log Kow value of 3.28;
- The calculation of the refined Fpen was determined using market research data and was therefore not acceptable.

2.3.6. Discussion on non-clinical aspects

The non clinical programme considered the CHMP guideline on the non-clinical development of fixed combinations of medicinal products (CPMP/SWP/258498/2005) and has been limited to 2 non clinical studies characterising the pharmacology and toxicology profiles of the use of the combination. All other submitted were derived from the literature. The CHMP accepted this approach since this application relates to a fixed combination (memantine 20 mg/donepezil 10 mg) that included compounds for which there was sufficiently documented human experience of their individual and combined use.

In line with effects of other NMDA antagonists, available preclinical data suggested that memantine increased the synaptic levels of ACh. An effect, which would not be detected by microdialysis method unless AChEs were inhibited. Additionally, ACh levels may be increased by different mechanisms, where memantine increases the release and donepezil reduce the degradation.

Toxicological data were limited to 28 days and showed a slight dose-dependent increase of vacuoles with memantine. A dose-dependent increase in exposure was found as memantine dose increased. Donepezil seemed to potentiate the memantine effect as with the 30 mg/kg dose of memantine alone no vacuoles were observed but at the same dose in combination with donepezil, vacuolation was observed in 1/10 animals. The exposures at which mortality was observed were lower than those at which neurodegeneration was reported. Taken together, mortality in the single dose toxicity study occurred at exposures 16 (donepezil) or 54 times (memantine) the human exposure based on Cmax or 6 (donepezil) or 10 times (memantine) the human exposure based on AUC. The safety margins based

on the highest oral dose without mortality were therefore 10 (donepezil) or 35 (memantine) based on Cmax and 5 (donepezil) or 19 (memantine) based on AUC. Neurotoxicity was observed in the groups receiving memantine and donepezil at doses of 30/0, 60/0, 60/5, 30/10 and 60/10 mg/kg orally or at a dose of 30/10 mg/kg i.p, therefore in all groups receiving memantine at doses of 30 mg/kg or above, irrespective of donepezil co-administration. A potentiation of neurodegeneration regarding the number of brain regions affected and the severity of findings was mainly seen in the groups receiving the combination at 60/10 mg/kg memantine/donepezil orally and in the group receiving memantine/donepezil at a dose of 30/10 mg/kg i.p, i.e. at exposures well exceeding the clinically relevant exposure. The No Observed Adverse Effect Level (NOAEL) for neurodegeneration under the conditions of this study was 8/5 mg/kg memantine/donepezil. Mortality in the repeated dose toxicity study occurred in 1/1/3 animals at doses of memantine and donepezil at 30/3, 60/0 and 60/10 mg/kg/day. No mortality was seen in the groups receiving the combination at 30/0, 30/10 or 60/3 mg/kg/day suggesting a lack of apparent dose-response relationship for the observed mortality at 30/3 or 60/0 mg/kg memantine/donepezil. Furthermore, there were no clinical signs except for chromodacryorrhea at 60/0 mg/kg/day and no significant effects on body weight were seen in any group. The NOAEL for mortality was considered 30/10 or 60/3 mg/kg/day, based on the lowest dose level causing mortality (60/10 mg/kg/day). Neurotoxicity was seen in 2 out of 10 rats at 60/10 mg/kg/day, and in 1 rat from each of the groups receiving 30/10, 60/0 and 60/3 mg/kg/day memantine in combination with donepezil. The minimal dose of the memantine/donepezil combination causing neurotoxicity was 30/10 mg/kg/day or 60/3 mg/kg/day. Consequently, the NOAELs for neurotoxicity was considered at 30/3 or 10/10 mg/kg/day.

Overall, the calculated safety margins were found to be sometimes low for one component when the exposure to the second one was high, and taking into account the proposed chronic clinical use of Acrescent. These data could not rule out possible toxic effects in humans at the proposed clinical dose level. During the evaluation, on the basis of these data and the safety profile of the combination, a recommendation was given by the CHMP to complement the toxicological programme with a 3 month toxicity study. However this recommendation was not followed by the applicant on the basis that the absence of a 3 months repeat dose toxicity study could be accepted if there was experience of concomitant use according to the guideline on the non-clinical development of fixed combinations of medicinal products (CPMP/SWP/258498/2005). In this regard, the CHMP took into account the clinical safety database including 24 clinical studies (of longer duration than 3 months) and a total of 1626 patients treated with a combination of donepezil and memantine, resulting in a total exposure for the combination of 1523 years and concluded that the applicant justification was acceptable.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of the combination have been adequately documented and meet the requirements to support this application. However, The CHMP could not conclude on whether or not the combination could pose a risk for the environment since some issues remained unresolved at this time.

2.4. Clinical aspects

The clinical program considered the CHMP Guideline on the Clinical Development of Fixed Medicinal Products (CPMP/EWP/240/95, Rev 1) and consisted of:

- A bioequivalence study (**Study 13458A**) that was conducted for the new fixed-combination tablet versus memantine and donepezil tablets taken in combination.

- An interaction study (**Study MEM-PK-07**) that was a single-centre, open-label, multiple-dose trial in healthy men and women. The primary objective of the study was to determine whether there is an in vivo pharmacokinetic interaction between memantine and donepezil.

- Twenty five clinical studies, 7 of them randomised, double-blind, placebo-controlled studies with memantine including patients (or a subset of patients) concurrently treated with memantine and donepezil. Of these 7 studies, one (**Study MEM-MD-02**) was designed to assess the effects of memantine added to ongoing treatment with donepezil in patients with moderate to severe AD.

- Treatment guidelines and literature to assess the medical environment and current practice for combination treatment, particularly with respect to when and why physicians prescribe combination treatment.

- Epidemiological studies and prescription databases have been evaluated to document the evidence of the widespread use of memantine and donepezil in combination in the European Union.

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies – Table 1

Table 1

Table 1 Biopharmaceutic Study

Study, Status, Report Location (Module 5)	Type of Study Study Design & Type of Control	FSFV/LSLV Number & Location of Sites	Number of Subjects Treated/Completed Age (mean), Sex	Diagnosis & Main Inclusion Criteria	IMPs: Dose, Route, & Regimen	Duration of Treatment	Primary Endpoints
13458A Completed	*Bioequivalence* Randomised, open-label, two-sequence, single-dose, crossover	Aug 2010/Oct 2010 1 site in UK	29/21 21 to 52 (31) years 20M/9F	Healthy men and women, aged ≥18 and ≤55 years	MEM: 20mg DPZ: 10mg Orally	2 single doses	To evaluate the bioequivalence of the MEM/DPZ combination tablet and the MEM and DPZ tablets taken together

Table 2 Pharmacokinetic and Pharmacodynamic Study

Study, Status, Report Location (Module 5)	Type of Study Study Design & Type of Control	FSFV/LSLV Number & Location of Sites	Number of Subjects Treated/Completed Age (mean), Sex	Diagnosis & Main Inclusion Criteria	IMPs: Dose, Route, & Regimen	Duration of Treatment	Primary Endpoints
MEM-PK-07 Completed	*Pharmacokinetics and pharmacodynamics* Multiple-dose, open-label	Jul 2001/Sep 2001 1 site in US	24/19 18 to 35 (27.6) years 16M/8F	Healthy subjects	MEM: 10mg once daily DPZ: 5 or 10mg once daily Orally	43 days	To evaluate whether there is an *in vivo* pharmacokinetic interaction between memantine and donepezil

2.4.2. Pharmacokinetics

No phase I clinical pharmacology studies specifically investigating absorption, distribution, metabolism, elimination (ADME) of the combination (memantine/donepezil) has been conducted. The pharmacokinetic studies consisted of one study investigating the drug interaction profile between the individual components of the fixed combination and another study evaluating the bioequivalence of the fixed combination and the both individual components taken together.

Plasma concentrations of memantine and donepezil were determined using LC/MS/MS methods. Pharmacokinetic parameters were determined using non compartmental methods. The AChE activity and inhibition of AChE by donepezil in red blood cells (RBCs) were measured using a validated radioenzyme assay.

The pharmacokinetic profile is well known for the individual components and is briefly presented below.

2.4.2.1. ***Absorption***

Memantine

Memantine is well absorbed, with high bioavailability approaching 100%. There is no indication that food influences the absorption of memantine.

Donepezil

Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. Food did not affect the absorption of donepezil hydrochloride.

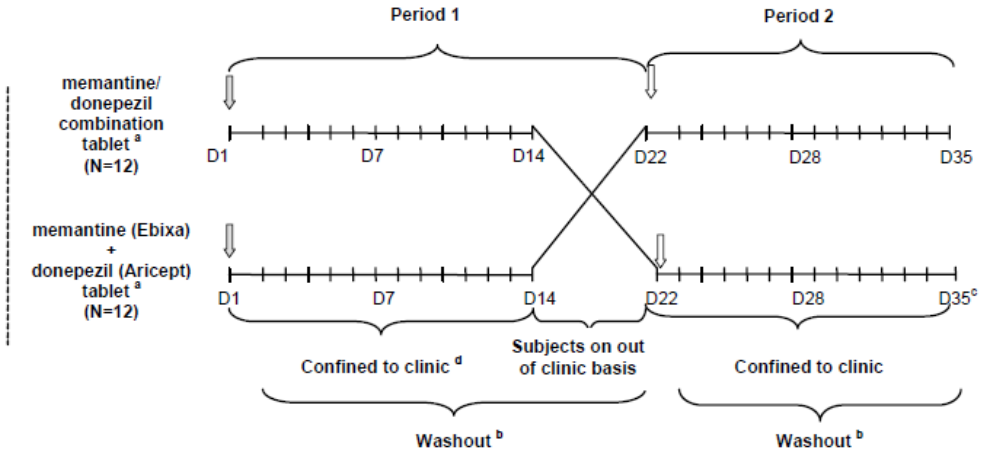
2.4.2.2. ***Bioequivalence***

Methods

Study design

Study 13458A was a single-centre, randomised, open-label, crossover, bioequivalence, single-dose study. Treatment consisted of two separate single-dose administrations of 20 mg memantine and 10 mg donepezil under fasting conditions. All subjects were to receive both the test and the reference treatment. The doses were separated by a washout period of 21 to 23 days (see Figure 1).

Figure 1



Treatment administration (Day 1, Period 1 and Day 22, Period 2)

The study was conducted in Covance Clinical Research Unit Ltd, United Kingdom. The bioanalytical, pharmacokinetics and statistical facilities were part of H. Lundbeck A/S, Denmark.

Blood samples (2 mL) for pharmacokinetic assessments were drawn at pre-dose, and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 264, and 312 hours post-dose (Periods 1 and 2). Samples were inverted 6 to 8 times and placed on water ice, and were centrifuged (1500 g for 10 min at approximately 4 ºC) within 30 minutes of collection. The samples were frozen at -20 ºC within 2 hours of collection. Samples were shipped frozen packed with sufficient quantities of dry ice to ensure that they remained frozen during transportation.

Test and Reference products

These are presented in Table 2.

Table 2

Tablet	Batch Number	Expiry Date
20 mg memantine/10 mg donepezil combination tablet	4320203T	Jan 2011
20 mg memantine tablet	91250	Dec 2010
10 mg donepezil tablet	100543	Dec 2010

Population studied

A total of 24 men and women (approximately equal numbers of men and women) aged between 18 and 55 years inclusive, with a body mass index (BMI) between 19 and 30 kg/m2 inclusive were planned for enrolment.

A total of 29 subjects were randomised into the study. A total of 21 subjects completed the study. Eight subjects (all women) withdrew due to adverse events.

The following subjects withdrew in Period 1:

- 2 subjects who received the test treatment in Period 1 both withdrew on Day 1, due to adverse events of vomiting.
- 3 subjects who received the reference treatment in Period 1, 2 withdrew due to adverse events of vomiting and 1 withdrew due to upper abdominal pain on Days 1, 1, and 4, respectively.

The following subjects withdrew in Period 2:

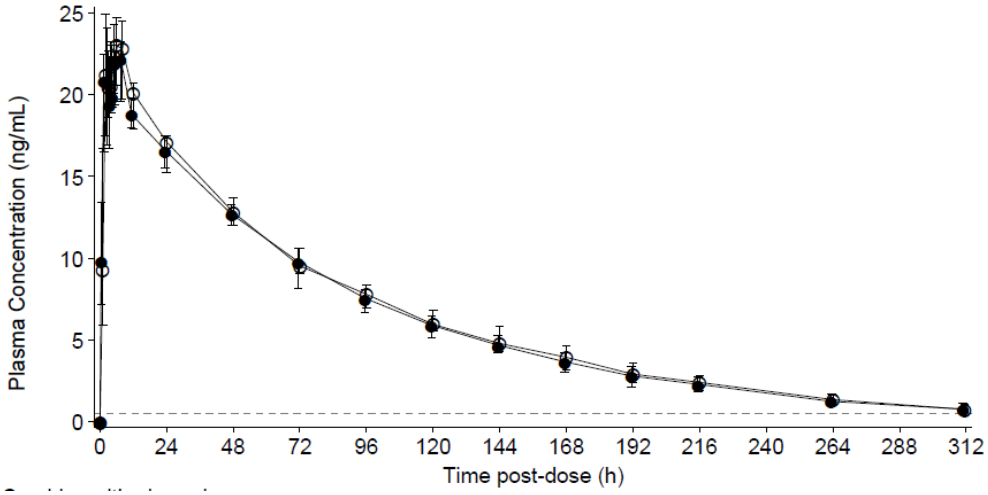
- 1 subject, who received the reference treatment in Period 1 and the test treatment in Period 2, withdrew due to an adverse event of upper abdominal pain on Day 27 (Period 2).
- 2 subjects, who received the test (Period 1) and the reference (Period 2) treatment; withdrew due to adverse events of paraesthesia and upper abdominal pain; on Days 28 and 23, respectively.

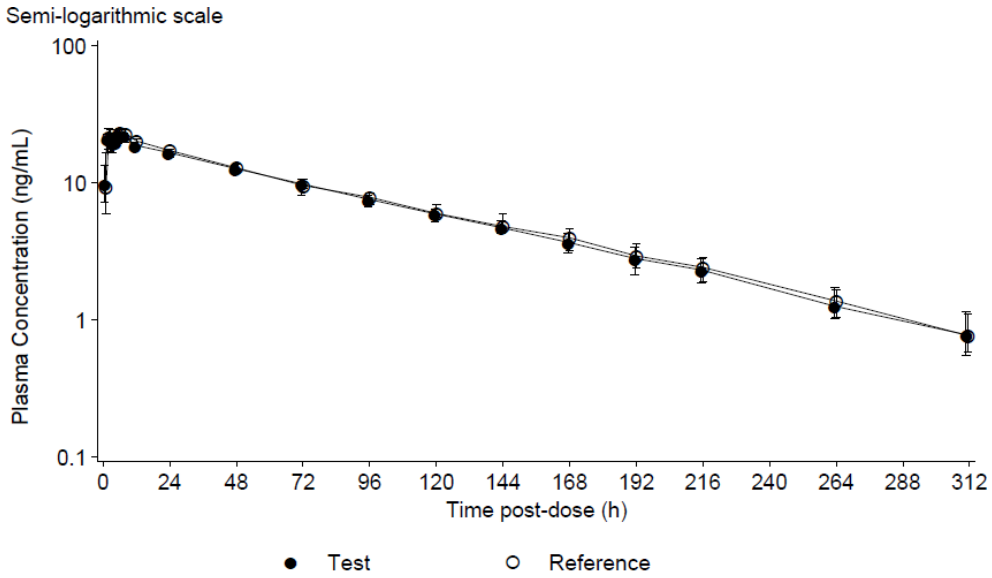
All subjects who withdrew in Period 1 were replaced. None of the subjects who withdrew in Period 2 were replaced.

Results

These are presented in Figures 2-5 and Table 3-4.

Figures 2 and 3. Median (and Quartiles) Plasma Concentrations of Memantine Following the Single-dose Administration of 20 mg Memantine and 10 mg Donepezil as a Combined Tablet (Test) and as Individual Tablets (Reference)





Figures 4 and 5. Median (and Quartiles) Plasma Concentrations of Donepezil Following the Single-dose Administration of 20 mg Memantine and 10 mg Donepezil as a Combined Tablet (Test) and as Individual Tablets (Reference)

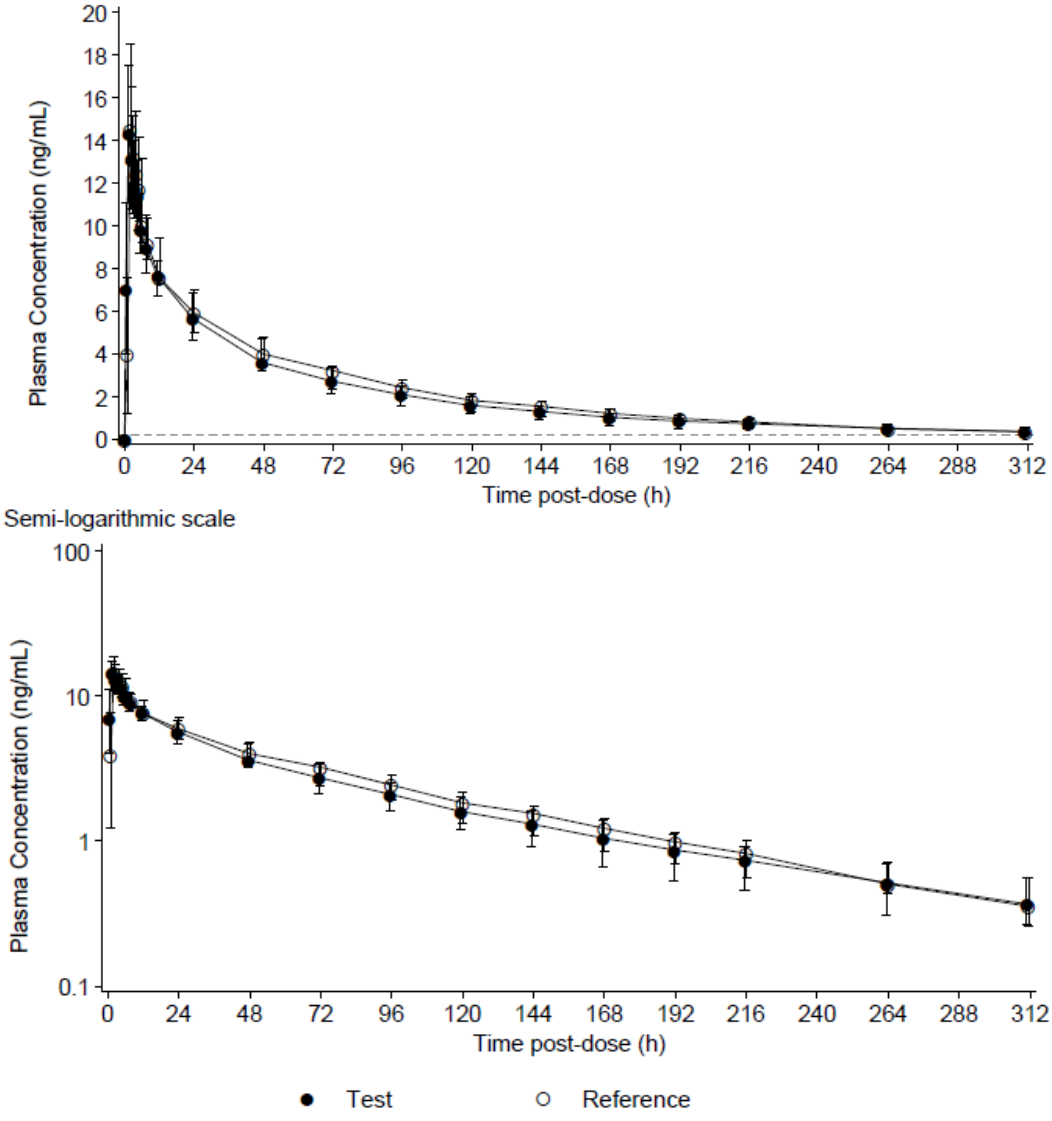


Table 3 .Pharmacokinetic parameters of memantine (completer set)

Parameter	20 mg Memantine/ 10 mg Donepezil Combined Tablet (Test) N = 21	20 mg Memantine/ 10 mg Donepezil Individual Tablets (Reference) N = 21	Estimated Ratio (90% CI)#
$AUC_{0\text{-}72\ h}$ (ng·h/mL)[a]	1055 (11.7)	1081 (13.3)	97.7 (95.3, 100.1)
C_{max} (ng/mL)[a]	23.5 (13.6)	24.4 (16.1)	96.4 (93.1, 99.9)
$AUC_{0\text{-}inf}$ (ng·h/mL)	2009 (16.5)	2088 (16.0)	96.0 (93.1, 99.0)
$AUC_{0\text{-}t}$ (ng·h/mL)	1917 (15.4)	1994 (15.7)	96.0 (93.2, 98.8)
$AUC_{\%extrap}$ (%)	4.43 (35.9)	4.43 (40.3)	NC
t_{max} (h)[a]	5.00 (2.00, 8.00)	6.00 (1.00, 8.00)	107.2
$t_{½}$ (h)	67.1 (13.8)	67.1 (14.3)	100.0
CL/F (L/h)	10.2 (16.3)	9.81 (16.2)	104.2
V_z/F (L)	973 (11.9)	938 (13.3)	104.2

Arithmetic mean (CV%) values are presented for $AUC_{0\text{-}72\ h}$, C_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $AUC_{\%extrap}$, $t_{½}$, CL/F, and V_z/F.
Median (min, max) values are presented for t_{max}.
N = number of subjects
NC = not calculated
# CIs are presented for primary pharmacokinetic parameters.
a N = 23

Table 4. Pharmacokinetic parameters of donepezil (completer set)

Parameter	20 mg Memantine/ 10 mg Donepezil Combined Tablet (Test) N = 21	20 mg Memantine/ 10 mg Donepezil Individual Tablets (Reference) N = 21	Estimated Ratio (90% CI)#
$AUC_{0\text{-}72\ h}$ (ng·h/mL)	401 (24.9)	418 (23.6)	95.5 (93.5, 97.6)
C_{max} (ng/mL)[a]	15.5 (23.6)	17.2 (26.7)	90.6 (85.4, 96.2)
$AUC_{0\text{-}inf}$ (ng·h/mL)[a]	762 (42.1)	790 (35.8)	95.0 (92.1, 97.9)
$AUC_{0\text{-}t}$ (ng·h/mL)	692 (35.1)	728 (31.9)	94.4 (91.8, 97.1)
$AUC_{\%extrap}$ (%)	7.48 (73.0)	6.95 (64.5)	NC
t_{max} (h)[a]	2.00 (1.00, 5.00)	2.00 (1.00, 5.00)	103.9
$t_{½}$ (h)	79.8 (28.5)	78.9 (26.3)	100.5
CL/F (L/h)	14.9 (33.0)	14.1 (33.0)	105.3
V_z/F (L)	1610 (21.9)	1521 (23.2)	105.9

Arithmetic mean (CV%) values are presented for $AUC_{0\text{-}72\ h}$, C_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $AUC_{\%extrap}$, $t_{½}$, CL/F, and V_z/F.
Median (min, max) values are presented for t_{max}.
N = number of subjects
NC = not calculated
# CIs are presented for primary pharmacokinetic parameters.
a N = 23

2.4.2.3. ***Distribution***

Memantine

Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 µmol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (CSF)/serum ratio of 0.52 was calculated. The volume of distribution is around 10 l/kg. About 45% of memantine is bound to plasma-proteins.

Donepezil

The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of 14C-labeled donepezil hydrochloride, approximately 28% of the label remained unrecovered. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known.

2.4.2.4. ***Elimination***

Memantine

Memantine is mainly excreted unchanged in the urine (60-80%) and its terminal half-life is 60 to 100 h. In volunteers with normal kidney function, total clearance (Cltot) amounts to 170 ml/min/1.73 m^2 and part of total renal clearance is achieved by tubular secretion.

Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 (see section 4.4). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers.

Donepezil

Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

2.4.2.5. ***Dose proportionality and time dependencies***

Memantine

Cmax following a single 20 mg oral dose of memantine ranges between 22 and 46 ng/ml. Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg.

Donepezil

Plasma concentrations and area under the curve rise in proportion to the dose.

2.4.2.6. ***Special populations***

No pharmacokinetic studies in special population have been performed with the combination (memantine/donepezil).

2.4.2.7. ***Pharmacokinetic interaction studies***

Study MEM-PK-07 was a single-centre, open-label, multiple-dose study in healthy men and women. The primary objective of the study was to determine whether there is an in vivo pharmacokinetic interaction between donepezil on memantine. The secondary objective was to determine whether co-administration of memantine affects the ability of donepezil to inhibit AChE activity in RBCs

For all subjects: on Day 1, a single dose of 10 mg memantine was administered. After a 14-day washout period, 5 mg/day donepezil for 7 days (Days 15 to 21) and then 10 mg/day donepezil for 22

days (Days 22 to 43). In the morning of the last day of donepezil treatment (Day 43), 10 mg memantine was also given.

Twenty-four subjects (16 males and 8 females) were enrolled and 19 subjects completed the study. Results are shown in Tables 5 and 6.

Table 5. Comparative pharmacokinetic profile of memantine when administered alone or with donepezil at Day 1

Parameter	Without Donepezil (N = 19)	With Donepezil (N = 19)
C_{max} (ng/mL)	12.8 ± 2.4	13.0 ± 2.0
t_{max} (h)	6.5 ± 2.1	6.5 ± 1.3
AUC_{0-t} (ng·h/mL)	958 ± 147	1003 ± 143
AUC_{0-inf} (ng·h/mL)	1125 ± 211	1188 ± 223
$t_{½}$ (h)	70.9 ± 24.1	72.3 ± 16.3
CL/F (mL/min)	127 ± 23.8	120 ± 21.2
V_z/F (L)	760 ± 202	735 ± 128
MRT (h)	98.9 ± 29.8	101 ± 19.5
Arithmetic mean (± SD) values are presented.		

The 90% CIs for the least squares means ratios for the log-transformed Cmax, AUC0-t, and AUC0-inf for memantine were within the acceptance range of 80% to 125% (CI:98.6-105.4; 101.6-108.1, and 102-109.7, respectively). These data indicated that multiple daily dosing with 10mg donepezil did not significantly affect the rate or extent of absorption of a single dose of 10mg memantine.

Table 6 Comparative pharmacokinetic profile of donepezil when administered alone or with memantine at Day 42

Parameter	Without Memantine (N = 19)	With Memantine (N = 19)
C_{max} (ng/mL)	49.1 ± 14.5	55.4 ± 18.0
t_{max} (h)	3.4 ± 1.5	3.3 ± 1.7
AUC_{0-24h} (ng·h/mL)	858 ± 247	934 ± 250
CL/F (mL/min)	215 ± 175	182 ± 91.5
Arithmetic mean (± SD) values are presented.		

The 90% CI for the least squares means ratio for the log-transformed AUC0-24h for donepezil was within the acceptance range of 80% to 125% (CI:105.1-117.3), indicating that single dosing with 10 mg memantine did not significantly affect the extent of absorption of multiple doses of 10 mg donepezil. However, the 90% CI for the least squares means ratio for the log-transformed Cmax was outside the acceptance range (104.2-126.5%). A re-analysis was performed excluding 4 subjects who did not attained steady state by Day 42 and both 90%CI for the least squares means ratio for the log-transformed AUC0-24h and Cmax were found within the acceptance range (CI:99.7-124.8; 101.8-116.6, respectively).

2.4.2.8. ***Pharmacokinetics using human biomaterials***

No pharmacokinetic studies using human biomaterials have been performed with the combination (memantine/donepezil).

2.4.3. Pharmacodynamics

2.4.3.1. *Mechanism of action*

Acrescent is a combination product containing two compounds with different mechanisms of action considered as “complementary”: memantine is an NMDA receptor antagonist and donepezil belongs to the class of acetylcholinesterase inhibitors. This combination product is claimed to be commonly used as therapy for the treatment of moderate to moderately severe Alzheimer's disease. Acrescent is intended to simplify the treatment regimen for patients who are already on a stable daily dose of 20 mg memantine and 10 mg donepezil. This would provide the opportunity to improve patient compliance and persistence with the treatment.

Memantine

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia. Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Donepezil

Donepezil is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is in vitro over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

2.4.3.2. *Primary and Secondary pharmacology*

No primary and secondary pharmacology studies in man have been performed with the combination (memantine/donepezil). However the pharmacodynamic interaction profile was studied in the study MEM-PK-07, previously described (see 2.4.2.7). Results are presented in Table 7.

Table 7 Comparative pharmacodynamic profile of donepezil when administered alone (Day 42) or with memantine (Day 43)

Parameter	Without Memantine (N = 19)	With Memantine (N = 19)
I_{max} (% of baseline)	77.8 ± 7.3	81.1 ± 5.7
AUC_I (% of baseline·h)	1708 ± 191	1785 ± 169
Arithmetic mean (± SD) values are presented.		

The 90% CIs for the least squares means ratios for the log-transformed Imax and AUCI were within the acceptance range of 80% to 125% (CI:101.8-107.1;102.7-106.9, respectively) indicating that inhibition of RBCs AChE activity was not significantly affected by co-administration of donepezil and memantine compared to administration of donepezil alone.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic data provided considered the CHMP Guideline on the Clinical Development of Fixed Medicinal Products (CPMP/EWP/240/95, Rev 1) and consisted of bioequivalence study (13458A) between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination) together with an interaction

study (MEM-PK-07) to evaluate pharmacokinetic interaction between memantine and donepezil and also examine the pharmacodynamic effect of memantine co-administration on the potential inhibition of AChE activity by donepezil in RBCs. According to the applicant, both memantine and donepezil were considered Biopharmaceutics Classification System (BCS) class I substances (high solubility and high absorption). The pharmaceutical form of the proposed fixed combination tablet is an immediate-release tablet for oral administration. The excipients in the formulation were considered all well-established excipients and similar to those used in the reference products.

Bioequivalence was demonstrated between the fixed combination applied for (memantine 20 mg/donepezil 10 mg) and the free combination of the recognised reference formulations of memantine 20 mg and donepezil 10 mg.

When a single dose of memantine was administered alone or in combination with donepezil (10 mg/day), donepezil did not show an effect on the pharmacokinetics of memantine. The % maximum inhibition of AChE activity from baseline averaged from 77.8% to and 81.1% for donepezil when administered with or without memantine suggesting no pharmacodynamic interaction between the 2 components when concomitantly used. Since the two compounds share different metabolic pathways, no metabolic interaction between memantine and donepezil was expected. Hence the CHMP considered acceptable that the design of this study did not investigate the interaction effect with memantine at steady state.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of the combination in human studies has been adequately documented and meet the requirements to support this application.

2.5. Clinical efficacy

Twenty five clinical studies, 7 of them randomised, double-blind, placebo-controlled studies with memantine including patients (or a subset of patients) concurrently treated with memantine and donepezil were submitted to support the clinical efficacy of the fixed combination (memantine 20 mg/donepezil 10 mg) in the indication applied for (moderate to moderately severe AD). Of these 7 studies, one (Study MEM-MD-02) was designed to assess the effects of memantine added to ongoing treatment with donepezil in patients with moderate to severe AD.

In addition, a bibliographical analysis was submitted to claim a widespread use of the combination (memantine/donepezil) and support the reduced amount of clinical data submitted in this application. This analysis consisted of available treatment guidelines/expert panel recommendations, published studies (including clinical, observational and market research data) and included a review of epidemiological, market research and prescription data.

2.5.1. Dose response study

No dose response study has been performed with the combination (memantine/donepezil).

2.5.2. Main studies

A tabular overview of the 7 clinical studies is presented in Table 8.

Table 8

Panel 1 Overview of Randomised, Double-blind, Placebo-controlled Studies in AD

Study ID	Study Duration and MEM Dose	AD Severity	Number of Patients Treated	
			PBO/AChEI (Number of Patients on DPZ)	MEM/AChEI (Number of Patients on DPZ)
DPZ – a pre-requisite				
MEM-MD-02	24 weeks, MEM 20 mg/day, ongoing treatment with DPZ	Moderate to severe (MMSE: ≥5 to ≤14)	201 (201)	202 (202)
AChEIs – a pre-requisite				
MEM-MD-12	24 weeks, MEM 20 mg/day, ongoing treatment with any AChEI	Mild to moderate (MMSE: ≥10 to ≤22)	216 (137)	217 (154)
MEM-MD-23	12 weeks, MEM 20 mg/day, ongoing treatment with any AChEI	Moderate to severe (with symptoms of agitation) (MMSE: ≥3 to ≤18)	17 (14)	17 (17)
AChEIs – allowed			**PBO (Number of Patients on DPZ)**	**MEM (Number of Patients on DPZ)**
10158[a]	24 weeks, MEM 20 mg/day, ongoing treatment with any AChEI (DPZ, GAL, or RIV)	Moderate to severe (with behavioural symptoms) (MMSE: ≥5 to ≤15)	187 (78)	182 (68)
MEM-MD-22	24 weeks, MEM 20 mg/day, nursing home residents	Moderate to severe (MMSE: ≥5 to ≤18)	132 (47)	133 (49)
MEM-MD-71	12 weeks, MEM 20 mg/day	Moderate (MMSE: ≥10 to ≤19)	129 (39)	135 (44)
10112	52 weeks, MEM 20 mg/day	Moderate (MMSE: ≥12 to ≤20)	144 (65)	133 (57)

MEM: memantine; PBO: placebo; AChEI: acetylcholinesterase inhibitor; DPZ: donepezil; GAL: galantamine; RIV: rivastigmine

a The original protocol for Study 10158 (07-Jul-2003) allowed concomitant treatment with AChEIs. Substantial Protocol Amendment SA07 (04-Sep-2009) changed this to a pre-requisite. The study was terminated, and only a few patients were enrolled in the study after the amendment came into effect.

1) STUDY MEM-MD-02

This was a prospective randomized, double-blind, placebo-controlled, parallel group, fixed-dose trial in which patients with moderate to severe AD were assigned to memantine/donepezil treatment or placebo/donepezil treatment for 24 weeks.

Method

Inclusion criteria

Patients with a diagnosis of probable Alzheimer's disease consistent with National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria, a magnetic resonance imaging (MRI) or computerised tomography (CT) scan within the past 12 months with results consistent with the diagnosis of probable Alzheimer's disease, and a Mini Mental State Examination Score (MMSE) of 5 to 14 at both screening and baseline were included. Ongoing daily donepezil therapy for more than 6 months before entrance into the trial and at a stable dose (5-10 mg/day) was required.

Outcomes/endpoints

The two primary efficacy parameters were the changes from baseline to Week 24 in the total Severe Impairment Battery (SIB Total score, a scale developed for the evaluation of the severity of cognitive dysfunction) and the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL modified score, focused on the performance of activities of daily living) on the ITT population and using the last observation carried forward (LOCF) approach. The modified ADCS-ADL is a 19-item subset of the 42-item scale.

Secondary efficacy parameters included the following: CIBIC-Plus score (Clinician's Interview-based Impression of Change – Plus version), total NPI (Neuropsychiatric Inventory score and subscales, FAST (Functional Assessment Staging), total BGP (Behavioral Rating Scale for Geriatric Patients) score and BGP care dependency and BGP cognitive subscales.

Results

Out of 404 patients randomized, 403 patients received double-blind treatment. Among these patients, 197 in the placebo/donepezil treatment group and 198 in the memantine/donepezil treatment group were included in the ITT population.

There were no clinically important differences between the treatment groups with regard to baseline demographic characteristics or disease severity. The study population was 65% female and 91% Caucasian. The mean patient age was 76 years. Mean MMSE score at baseline was 10.

At Week 24, a statistically significant and clinically relevant benefit for memantine/donepezil treatment relative to placebo/donepezil treatment was observed for the modified ADCS-ADL, SIB, and CIBIC-Plus scores. Patients treated with memantine/donepezil demonstrated a numerical improvement in cognitive performance scores relative to baseline values over the 24-week course of the study, whereas patients receiving placebo/donepezil exhibited progressive cognitive decline over the same period. Results from other secondary efficacy parameters, including the BGP and the NPI, provided further evidence for the efficacy of memantine in the treatment of moderate to severe dementia.

Results are presented in Tables 9 and 10.

Table 9

Panel 14. Summary of Efficacy Results			
Variable	*Placebo/ Donepezil*	*Memantine /Donepezil*	*p-value*
WEEK 24 (LOCF)			
SIB LS mean change	-2.5	0.9	<0.001
ADCS-ADL LS mean change	-3.4	-2.0	0.028
CIBIC-Plus mean	4.66	4.41	0.027
WEEK 24 (OC)			
SIB LS mean change	-2.4	1.0	<0.001
ADCS-ADL LS mean change	-3.3	-1.7	0.020
CIBIC-Plus mean	4.64	4.38	0.028
Cross reference: Tables 3.1, 3.2, and 3.3 ITT population			

Table 10

Panel 13. LS Mean Change from Baseline to Week 24 (LOCF) in Other Secondary Efficacy Parameters			
	Placebo/Donepezil	*Memantine/Donepezil*	*p value*
NPI	3.7	-0.1	0.002
FAST	0.4	0.4	0.990
BGP (Total)	3.3	1.1	<0.001
BGP (Care Dependency)	2.3	0.8	0.001
BGP (Cognitive)	0.5	0.2	0.035
Cross-reference: Tables 3.4 to 3.8.			

2) STUDY MEM-MD-12

This was a 24-week, randomised, double-blind, placebo-controlled, fixed-dose study evaluating the safety and efficacy of memantine (20 mg once daily) compared to placebo in patients with mild to moderate Alzheimer's Disease currently receiving AChE inhibitors for at least six months.

Method

Inclusion criteria

Patients with a primary diagnosis of probable AD, a baseline MMSE score ≥10 and ≤22, a baseline Hachinski Ischaemia Scale (HIS) score ≤4, and a CT or MRI performed ≤12 months prior to screening, confirming the diagnosis of probable AD were recruited. The patients were required to have a Montgomery and Åsberg Depression Rating Scale (MADRS) total score <22 at screening. The patients were required to have been on AChEI treatment (donepezil, rivastigmine, or galantamine) for ≥6 months prior to study start, and at a stable dose for ≥3 months.

Outcomes/endpoints

The primary efficacy analyses were the mean changes from baseline in AD Assessment Scale – Cognitive Subscale (ADAS-cog) total score and the mean CIBIC-plus score at Week 24, based on the ITT population and using the LOCF approach.

Results

A total of 427 patients were included in the ITT population: 214 in the memantine/AChEI group and 213 in the placebo/AChEI group. A total of 291 patients were on concurrent treatment with donepezil during the study: 154 (71%, all patients treated set: APTS) in the memantine/AChEI group and 137 (63%) in the placebo/AChEI group. The mean baseline ADAS-cog and CIBIC-plus scores were approximately 27 and 3.9, respectively, in both treatment groups. A total of 48 patients (11%, APTS) withdrew from the study: 23 (11%) in the memantine/AChEI group and 25 (12%) in the placebo/AChEI group.

The mean change from baseline in the ADAS-cog total score numerically favoured the memantine/AChEI-treated group compared to the placebo/AChEI-treated group at all visits, using the LOCF analysis. This between-treatment difference was not statistically significant.

Results are presented in Table 11.

Table 11

Table 11–1. Least Square Mean Change (SE) From Baseline in ADAS-cog

Timepoint	*Placebo*		*Memantine*		*LS Mean Difference*	*p-value*[a]
	N	*Mean*	*N*	*Mean*		
Baseline Mean ± SD	212	26.8 ± 9.88	212	27.9 ± 10.98		
Least Square Mean Change						
Week 24 LOCF *(SE)*	213	0.8 (0.45)	214	0.1 (0.45)	-0.7	0.184
Week 24 OC *(SE)*	188	0.8 (0.47)	192	0.0 (0.48)	-0.8	0.186

[a] p-value is based on the results of an ANCOVA model with treatment group and study center as factors, and Baseline value as covariate.
ITT Population.
Cross Reference: Section 14.1 Table 5.1.

There was no statistically significant difference between the memantine/AChEI-treated patients compared to the placebo-treated patients in the CIBIC-Plus score using either the LOCF or OC analysis.

3) Study MEM-MD-23

This was a 12-week, randomised, double-blind, placebo-controlled, fixed-dose study.

Method

Inclusion criteria

Patients aged ≥50 years, with a primary diagnosis of probable AD, a baseline MMSE score ≥3 and ≤18, and an NPI agitation/aggression score ≥4 at screening and baseline. Patients who were taking an atypical antipsychotic at baseline had to have been on a stable dose for >1month prior to enrolment. The patients were required to have been on stable treatment with AChEIs for ≥3 months prior to study start.

Outcomes/endpoints

The primary efficacy analysis was the mean change from baseline in NPI total score at Week 12, based on the ITT population and using the LOCF approach. The secondary efficacy analyses were based on the ADCS-ADL total score, NPI agitation/aggression score, Clinical Global Impression – Severity of Illness (CGI-S) and– Global Improvement (CGI-I) scores, Cohen Mansfield Agitation Inventory (CMAI) score, and Positive and Negative Syndrome Scale – Excited Component (PANSS-EC) score.

Results

The study was terminated due to poor patient enrolment. A total of 33 patients (of the 150 planned) were included in the ITT population: 17 in the memantine/AChEI group and 16 in the placebo/AChEI group. A total of 31 patients were on concurrent treatment with donepezil during the study: 17 (100%, APTS) in the memantine/AChEI group and 14 (82%) in the placebo/AChEI group. A total of 4 patients (12%, APTS) withdrew from the study: 2 (12%) in each treatment group. Because the study was terminated, no statistical analyses were performed, and no conclusions could be drawn.

4) Study 10158

This was a 24-week, randomised, double-blind, placebo-controlled, fixed-dose study examining the efficacy and safety of memantine in patients with moderate to severe dementia of the Alzheimer's type.

Method

Inclusion criteria

The patients were outpatients, aged ≥50 years, with a primary diagnosis of probable AD, a baseline MMSE score ≥ 5 and ≤ 15, a baseline HIS score ≤ 4, and an NPI total score ≥ 13 and NPI agitation/aggression score ≥1 at screening and baseline. The protocol was amended to make treatment with an AChEI a pre-requisite.

Outcomes/endpoints

The primary efficacy analyses were the mean changes from baseline in NPI total score and SIB total score at Week 24, based on the full analysis set (FAS) and using the LOCF approach. The secondary efficacy analyses included the CIBIC-plus score, ADCS-ADL total score, NPI single-item scores, CMAI score, Health Status Questionnaire (HSQ-12; patient and caregiver) scores, and Resource Utilization in Dementia (RUD) total score.

Results

A total of 324 patients (of the 450 planned) were included in the FAS: 159 in the memantine group and 165 in the placebo group. A total of 146 patients were on concurrent treatment with donepezil during the study: 68 (37%, APTS) in the memantine group and 78 (42%) in the placebo group. The

mean baseline NPI and SIB total scores were approximately 30 and 82, respectively, in both treatment groups. A total of 63 patients (17%, APTS) withdrew from the study: 31 (17%) in the memantine group and 32 (17%) in the placebo group. There were no statistically significant differences between the treatment groups on the NPI or the SIB total scores at Week 24.

Results are presented in Table 12 and 13

Table 12

Table 8 NPI Mean Total Score (FAS, LOCF)

Treatment Group	Week	n	Mean	SD	Median	Minimum	Maximum
PBO	Screen	165	30.72	13.99	27.00	5	71
	Baseline	165	29.18	13.27	26.00	7	80
	Week 4	161	23.17	13.01	20.00	0	61
	Week 8	162	23.06	15.66	20.00	0	72
	Week 12	162	22.04	15.04	19.00	1	72
	Week 18	162	23.43	16.18	20.00	0	69
	Week 24	162	22.31	16.28	19.00	0	72
MEM	Screen	159	31.75	14.05	30.00	9	87
	Baseline	159	30.94	14.79	26.00	5	89
	Week 4	156	27.50	15.76	23.00	0	89
	Week 8	156	24.59	17.13	21.00	0	89
	Week 12	156	23.90	16.53	20.00	0	77
	Week 18	156	24.60	16.98	21.50	0	95
	Week 24	156	23.77	15.64	20.00	0	77

DRAFT 10158 ET_NPI02_LOCF 18APR2011:13:45:45 1001/175 - TFL/SAD Build Numbers

Table 13

Table 10 SIB Mean Total Score (FAS, LOCF)

Treatment Group	Week	n	Mean	SD	Median	Minimum	Maximum
PBO	Baseline	165	81.98	12.86	85.00	22	98
	Week 12	155	81.03	15.48	86.00	12	100
	Week 24	158	80.01	16.04	84.00	21	100
MEM	Baseline	159	82.25	14.58	87.00	14	99
	Week 12	150	81.18	14.89	86.00	21	100
	Week 24	151	80.68	16.28	86.00	19	98

DRAFT 10158 ET_SIB02 18APR2011:13:46:35 1001/175 - TFL/SAD Build Numbers

5) Study MEM-MD-22

This was a 24-week, randomised, double-blind, placebo-controlled, fixed-dose study evaluating the effectiveness of memantine versus placebo with regard to behavioral symptoms, functional capabilities and overall quality of life in nursing home patients with moderate to severe AD.

Method

Inclusion criteria

Patients were aged ≥65 years, with a primary diagnosis of probable AD, a baseline MMSE score ≥5 and ≤18, and, if available, a CT or MRI performed prior to screening, confirming the diagnosis of probable AD. The patients were allowed to be on AChEI treatment prior to study start.

Outcomes/endpoints

No primary or secondary efficacy analyses were pre-specified. Analyses were performed on a number of Minimum Data Set (MDS; a standardised set of items, used to assess nursing home residents, addresses the residents' cognitive, behavioural, functional, and medical status) and non-MDS variables (NPI-nursing home or NPI-NH , CMAI, BGP, PANSS-EC, Multidimensional Observation Scale for Elderly Subjects (MOSES) – Withdrawal Behaviour subscale, and AD Cooperative Study – Clinical Global

Impression of Change or ADCS-CGIC) assessed at each visit, based on the ITT population and using the LOCF and OC approaches. The analyses were two-way analyses of covariance (ANCOVA) of memantine versus placebo at the 5% level of significance. A total sample size of 250 randomized patients was used for this study. The sample size was based upon clinical considerations judged to be reasonable for the exploratory objectives of this study.

Results

A total of 263 patients were included in the ITT population: 132 in the memantine group and 131 in the placebo group. A total of 96 patients were on concurrent treatment with donepezil during the study: 49 (37%, APTS) in the memantine group and 47 (36%) in the placebo group. The mean baseline scores for the non-MDS effectiveness variables were comparable between the two treatment groups. A total of 58 patients (22%, APTS) withdrew from the study: 29 (22%) in the memantine group and 29 (22%) in the placebo group.

At Week 24, there were improvements in both treatment groups in the non-MDS as well as the MDS effectiveness variables. There were no statistically significant differences between the treatment groups in any of the variables measured.

Results are presented in Table 14.

Table 14

Table 11.4.1.1–1. Least Square Mean Change From Baseline in non-MDS Effectiveness Variable Total Scores at Week 24 (LOCF)—ITT Population

	LS Mean (SE)		*LS Mean Difference (95% CI)*	*p-Value*
	Placebo (N = 131)	*Memantine (N = 132)*	*(Memantine –Placebo)*	
NPI-NH	–4.1 (1.3)	–2.7 (1.3)	1.4 [–1.7, 4.5]	0.370
CMAI	–1.6 (1.1)	–3.0 (1.1)	–1.4 [–4.0, 1.2]	0.290
BGP	1.6 (0.7)	0.9 (0.7)	–0.7 [–2.3, 0.9]	0.381
PANSS-EC	–0.8 (0.5)	–0.8 (0.5)	–0.0 [–1.1, 1.1]	0.986
MOSES	1.0 (0.4)	0.3 (0.4)	–0.7 [–1.8, 0.3]	0.155
ADCS-CGIC	3.8 (0.14)	3.6 (0.14)	–0.1 [–0.5, 0.2]	0.445

A negative change indicates improvement from baseline.

ADCS-CGIC is the change score.

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least square; MDS = minimum data set

Cross-reference: Table 14.4.1.1A, 14.4.1.2A, 14.4.1.3A, 14.4.1.4A, 14.4.1.5A, and 14.4.1.6C.

6) Study MEM-MD-71

This was a 12-week, randomised, double-blind, placebo-controlled, fixed-dose study evaluating the effect of memantine versus placebo on functional communication in patients with moderate AD.

Method

Inclusion criteria

The patients were outpatients, aged ≥50 years, with a primary diagnosis of probable AD, a baseline MMSE score ≥10 and ≤19, a baseline HIS score ≤4, and a CT or MRI performed ≤12 months prior to screening, confirming the diagnosis of probable AD. The patients were allowed to be on AChEI

treatment prior to study start, provided the dose had been stable for ≥3months, and remained fixed for the duration of the study.

Outcomes/endpoints

The primary efficacy analysis was the mean change from baseline in Functional Linguistic Communication Inventory (FLCI) total score at Week 12, based on the ITT population and using the LOCF approach. The analysis was a two-way ANCOVA of memantine versus placebo at the 5% level of significance. The secondary efficacy analysis was based on the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA-FACS) score.

Results

A total of 257 patients were included in the ITT population: 133 in the memantine group and 124 in the placebo group. A total of 83 patients were on concurrent treatment with donepezil during the study: 44 (33%, APTS) in the memantine group and 39 (30%) in the placebo group. The mean baseline FLCI score was approximately 68 in both treatment groups. A total of 14 patients (5.3%, APTS) withdrew from the study: 5 (3.7%) in the memantine group and 9 (7.0%) in the placebo group.

The mean change from baseline in FLCI total score at Week 12 (see Table 15) was numerically higher in the memantine group than in the placebo group, indicating a trend towards better response in favour of memantine treatment; the difference was not statistically significant.

Table 15

Panel 10 Change from Baseline in FLCI Total Score at Week 12 (LOCF, OC, and MMRM) – Study MEM-MD-71 (ITT Population)

	PBO[a]			MEM[a]			LS Mean Difference (95% CI)	ANCOVA p-value
	Baseline Score (SE)	n	LS Mean (SE)	Baseline Score (SE)	n	LS Mean (SE)		
Primary Analysis (LOCF)	67.8 (1.02)	124	-0.6 (0.59)	68.7 (0.97)	133	0.7 (0.57)	1.3 (-0.1; 2.8)	0.070
Sensitivity Analyses								
OC		119	-0.3 (0.59)		129	0.6 (0.56)	1.0 (-0.5; 2.4)	0.184
MMRM		119	0.1 (0.54)		129	1.3 (0.52)	1.2 (-0.2; 2.7)	0.097

LS: least squares; CI: confidence interval; MMRM: mixed model repeated measures

a Includes monotherapy and concurrent treatment with an AChEI

7) Study 10112

This was a 52-week, randomised, double-blind, placebo-controlled, fixed-dose study evaluating the effects of memantine on the rate of total brain atrophy in patients with probable moderate Alzheimer's disease over the course of treatment, using MRI technology.

Method

Inclusion criteria

The patients were outpatients, aged ≥50 years, with a primary diagnosis of probable AD, a baseline MMSE score ≥12 and ≤20, a HIS score ≤4 at screening and baseline, and an MRI performed prior to screening, confirming the diagnosis of probable AD. The patients were allowed to be on AChEI treatment prior to study start, provided the treatment had been ongoing for >6months, at a stable dose for >3months, and remained fixed for the duration of the study.

Outcomes/endpoints

The primary efficacy analysis was the direct change in total brain volume (TBV), as measured using the brain boundary shift integral (BBSI), at Week 52, based on the FAS-MRI and using the OC approach.

The analysis was based on a linear mixed model relating direct change in TBV to time and its interaction with treatment group. This model also included a time-by-AChEI group interaction as a fixed effect. The secondary efficacy analyses included the change in hippocampal volume atrophy rate, effects of memantine on cognitive and behavioural outcomes, and correlation between TBV atrophy rate and clinical outcomes.

Results

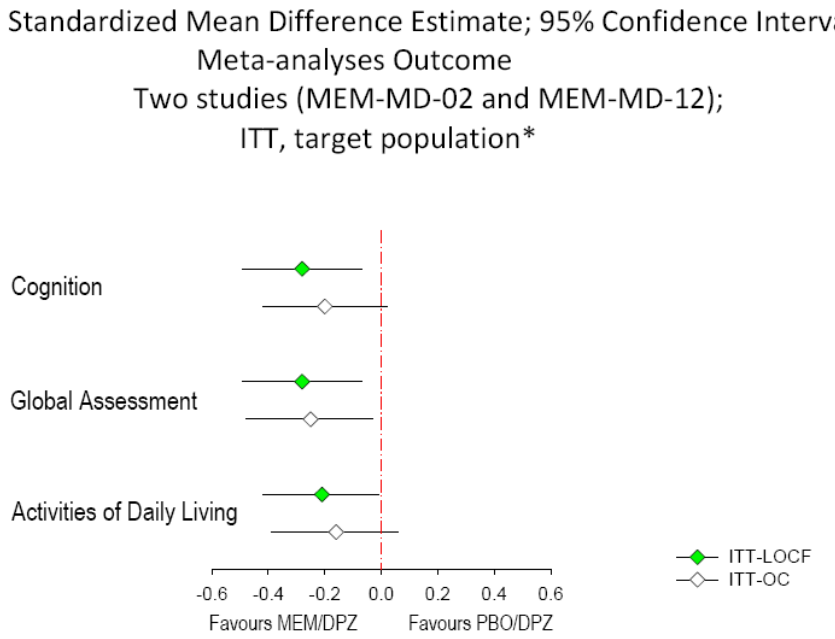
A total of 275 patients were included in the FAS: 133 in the memantine group and 142 in the placebo group. A total of 123 patients were on concurrent treatment with donepezil during the study: 57 (43%, APTS) in the memantine group and 65 (45%) in the placebo group. There were no clinically significant differences in baseline characteristics between the treatment groups. A total of 60 patients (22%, APTS) withdrew from the study: 30 (23%) in the memantine group and 30 (21%) in the placebo group. The primary analysis showed no statistically significant differences between the memantine and placebo groups in total brain atrophy rates.

2.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy of the combination over donepezil

Following CHMP request to further substantiate the efficacy of the combination, the applicant conducted a number of meta-analyses. Results are presented in Figures 6 and 7.

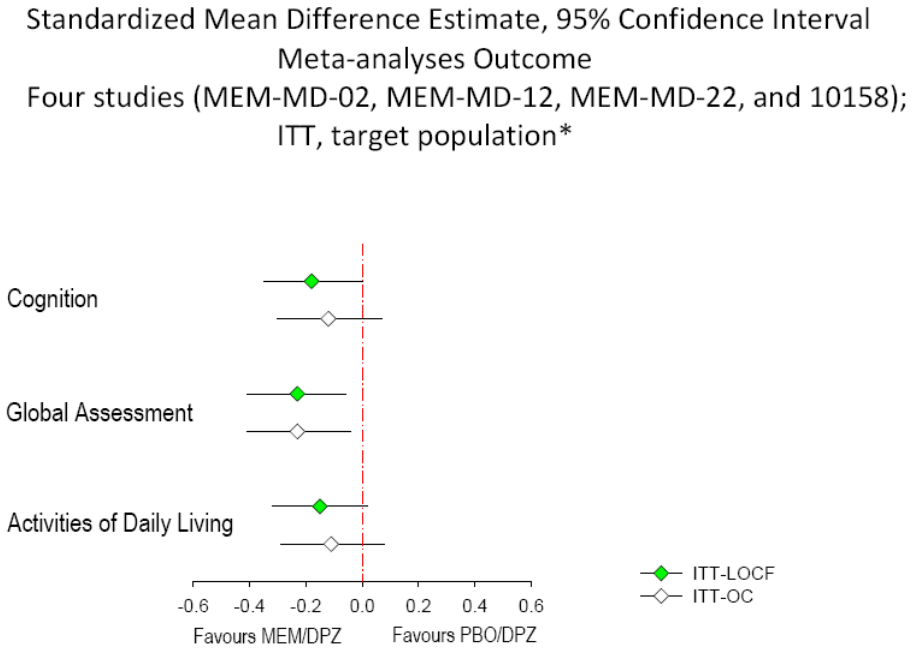
Figure 6: Summary of meta-analysis (2 studies, target population) with standardised mean differences for each of the three main Alzheimer's disease domains (cognition, global assessment, activities of daily living)



DPZ, donepezil; ITT, intention-to-treat; LOCF, last observation carried forward; MEM, memantine; OC, observed case; PBO,placebo.
* Target population (patients with MMSE score of 10 to 19) treated with 20 mg memantine/10 mg donepezil [MEM/DPZ] per day compared with placebo/10 mg donepezil [PBO/DPZ] per day.

Figure 7: Summary of meta-analyses (4 studies) with standardised mean differences for

each of the three main Alzheimer's disease domains (cognition, global assessment, activities of daily living)

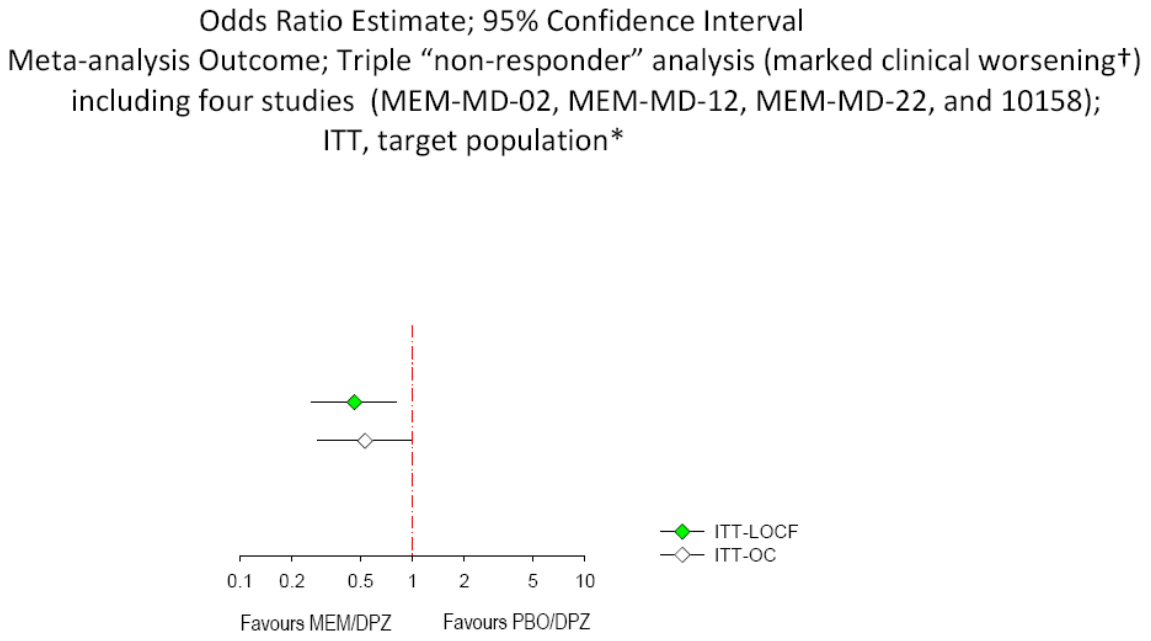


DPZ, donepezil; ITT, intention-to-treat; LOCF, last observation carried forward; MEM, memantine; OC, observed case; PBO,placebo.
* Target population (patients with MMSE score of 10 to 19) treated with 20 mg memantine/10 mg donepezil [MEM/DPZ] per day compared with placebo/10 mg donepezil [PBO/DPZ] per day.

2.5.4. Ancillary analysis

In addition to the meta-analyses provided, the applicant submitted a non-responder analysis to further support the efficacy of the combination. Results are presented in Figure 8.

Figure 8: Summary of Analyses on Marked Clinical Worsening ("Non-responder")



DPZ, donepezil; ITT, intention-to-treat; LOCF, last observation carried forward; MEM, memantine; OC, observed case; PBO,placebo.

* Target population (patients with MMSE score of 10 to 19) treated with 20 mg memantine/10 mg donepezil [MEM/DPZ] per day compared with placebo/10 mg donepezil [PBO/DPZ] per day.
† At study endpoint: marked clinical worsening in three Alzheimer's disease domains (cognition, global assessment and activities of daily living).

2.5.5. Clinical studies in special populations

No clinical studies in special populations have been performed with the combination (memantine/donepezil).

2.5.6. Supportive studies

The applicant submitted a bibliographical analysis to claim a widespread use of the combination (memantine/donepezil) and support the reduced amount of clinical data submitted in this application. This analysis consisted of available treatment guidelines/expert panel recommendations, published studies (including clinical, observational and market research data) and included a review of epidemiological, market research and prescription data.

In addition, following the CHMP reference to a recent publication from Howard et al. (2012), the applicant presented results of this study (DOMINO) as supportive of efficacy of the combination.

2.5.6.1. *Treatment guidelines / expert panel recommendations*

Treatment guidelines

These are presented in Table 16.

Table 16

Country	Guidelines for combination therapy of memantine and AChEIs
Austria	The combination therapy of memantine and AChEIs is desirable for patients with severe or moderate AD (MMSE benchmark 5-14). In a randomised study by Tariot et al., 2004 the combination of memantine and donepezil proved to be superior to monotherapy with donepezil. Furthermore open studies have shown that combination therapy with rivastigmine and memantine are also more effective than monotherapy alone. Another study reports the positive effect of combination therapy compared with the use of AChEIs alone over a period of several years.
Czech Republic	To improve the effect of AChEIs, memantine can be added - this combination, although expensive, is rational and evidencebased (e.g. the study of the Cummings et al., 2006), and is recommended in other guidelines for example the Italian Psychogeriatric Association guidelines, which are taken as a model for the therapy of dementia in the EU countries (Caltagirone et al., 2005). In the moderate stage of AD, AChEIs are still the leading pharmacological therapy, but it is possible to add memantine. Even in patients who had not taken AChEIs previously, it is possible to prescribe combination therapy, if the conditions of the health insurance agency for the using AChEIs and/or memantine are met.
Denmark	Combination therapy may be relevant in patients treated with ACHEIs with AD progressing to the moderate stage with a MMSE score of 10-14. Patients treated with ACHEIs in the moderate stage can be treated with a combination of an AChEI and Ebixa (memantine). When the disease has progressed to the severe stage treatment with Ebixa (memantine) as monotherapy is continued.
Finland	Use of combination therapy (memantine & AChEI) in moderate and severe AD might delay nursing home placement. Memantine combined to donepezil might decrease behavioral disturbances in some of moderate and severe AD patients. Memantine combined to AChEI in mild AD doesn't give any additional benefits.
France	Combination therapy (AChEI and memantine) was compared to monotherapy with AChEIs in 2 clinical trials with contradictory results. Based on presently available data, there are no arguments to recommend combination therapy.
Germany	An add-on treatment with memantine in patients treated with donepezil is superior to monotherapy with donepezil in severe Alzheimer's dementia (MMSE 5-9) - recommendation: can be done. An add-on treatment with memantine in patients with mild to moderate AD (MMSE 15-22) already treated with AChEIs has shown no superiority to a monotherapy with AChEIs. The combination is not recommended. For an add-on treatment with memantine in patients with moderately-severe AD (MMSE 10-14) already treated with AChEIs there is no convincing evidence. No recommendation can be given.
Hungary	Memantine therapy is indicated in severe AD (MMSE < 10) or in moderate AD (MMSE 18-11), either as an adjuvant therapy to AChEIs or, in case of inefficacy or intolerability of AChEIs, as a monotherapy. According to the preliminary results add on therapy of memantine in combination with an AChEI could be beneficial.
Iceland	No reference to combination treatment within the guidelines for dementia or AD.
Italy	Memantine is effective as an adjunct to donepezil in patients with moderate to severe AD.
Netherlands	No reference to combination treatment within the guidelines for dementia or AD.
Poland	Combination therapy (AChEIs and memantine) is one of the therapeutic options for treating AD.
Romania	For patients who progress from mild to moderate-stage AD (MMSE 14-20) memantine can be added (10-20 mg daily dose) to AChEI treatment, especially when rapid progression occurs. Memantine can be used in this situation as monotherapy, or as combination therapy. Patients with moderate-stage AD (MMSE 10-14) should be treated with a combination of AChEI and memantine.
Slovenia	No reference to combination treatment within the guidelines for dementia or AD.
Spain	In patients already receiving an AChEI, it is possible to add memantine.
Sweden	For patients with moderate to severe AD —adding memantine to treatment with an AChEI (donepezil) was recommended at level 6 out of 10 (with 1 being the strongest recommendation).
UK	Combination treatment with memantine and AChEIs cannot be recommended because there is a lack of evidence of additional clinical efficacy compared with monotherapy.

EFNS	The benefits of adding memantine to AChEIs are not clear, an early study of adding memantine to donepezil was positive, but a recent study of over 400 subjects which added the drug or placebo to those stable on any of the three AChEIs showed no evidence of benefit in either cognitive or non-cognitive symptoms. Further studies are needed before clear recommendations can be made about the benefits of adding memantine to AChEIs.

No guidelines relating to the treatment of dementia or AD in Belgium, Bulgaria, Cyprus, Estonia, Greece, Ireland, Latvia, Lithuania, Luxembourg, Malta, Norway, Portugal, Slovakia.

Expert-panel recommendations

Three additional guidelines that have been developed and published to assist health care professionals in the effective pharmacologic management of patients with AD, in order to optimise patient outcomes were identified from the literature search:

- The US Alzheimer's Disease Management Council Clinical Consensus Panel (ADMC, 2004). This algorithm indicated that memantine should be added when no stabilization or reduction in the rate of cognitive and functional decline is observed during AChEI monotherapy, despite dose optimization and switching strategies.
- The US Alzheimer's Drug Discovery Foundation (ADDF) panel–approved recommendations stated that for patients who progress from mild to moderate AD, memantine should be added to therapy with an AChEI.
- An educational supplement for Nurse Practitioners: the authors concluded that memantine and AChEI combinations appeared to be a well-tolerated, effective treatment strategy.

2.5.6.2. *Published studies*

Available literature data related to clinical trials and post-hoc analyses of memantine and donepezil combination therapy and observational studies for combination therapy with memantine and AChEIs are presented in Table 17.

Clinical trial data and post-hoc analyses

Table 17. Clinical trial data identified from the literature search

Author and Date	Title and overview of paper
Porsteinsson et al., 2008	Memantine treatment in patients with mild to moderate AD already receiving an AChEI: A randomized, double-blind, placebo-controlled trial.
Tariot et al., 2004	Memantine treatment in patients with moderate to severe AD already receiving donepezil: A randomized controlled trial.
Post-hoc analyses of Tariot et al., 2004 clinical trial	
Cummings et al., 2006	**Title:** Behaviour effects of memantine in AD patients receiving donepezil treatment.
	Results: Patients treated with combined therapy of memantine and donepezil had significantly lower NPI total scores than patients treated with placebo (donepezil only). Combination treatment reduced agitation/aggression, irritability and appetite/eating disturbances.
Feldman et al., 2006	**Title:** Activities of Daily Living in moderate to severe AD: An analysis of the treatment effects of memantine in patients receiving stable donepezil treatment.
	Results: Combination therapy of memantine and donepezil reduced the overall functional decline in moderate to severe AD patients compared with donepezil treatment alone.
Schmitt et al., 2006	**Title:** Cognitive response to memantine in moderate to severe AD patients already receiving donepezil.
	Results: Statistically greater effects of combination therapy over donepezil alone were seen in memory, language and praxis.
van Dyck et al., 2006	**Title:** A responder analysis of memantine treatment in patients with AD maintained on donepezil.
	Results: Memantine produced both improvement and stabilisation of symptoms, across multiple outcomes using ADCS-ADL19, SIB, CIBIC-Plus and NPI.

Observational studies and clinical effectiveness studies

Two studies conducted in a clinical practice setting specifically presented results in regard to memantine and AChEI combination therapy:

- Atri et al. (2008) conducted a long-term, real-world clinical effectiveness study that enrolled a prospective cohort of patients from a Memory Disorders Unit with a diagnosis of AD. Patients received either memantine plus an AChEI (n=116), an AChEI alone (n=122) or no treatment (n=144). Results showed that patients receiving combination therapy with memantine and an AChEI had significantly lower mean annualised rates of deterioration in two measures, the Blessed Dementia Scale (BDS) and Weintraub Activities of Daily Living Scale (ADL). These cognitive and functional benefits increased with time on treatment and were sustained for years.
- A recent (Lopez et al., 2009) retrospective, observational study in 943 patients with AD, with at least one year of follow-up data, showed that time to nursing home admission was significantly delayed in patients receiving memantine and AChEI combination therapy compared with those receiving AChEI monotherapy.

Market research studies

Two market research surveys (InforMed Insight and Adelphi Real World Disease Specific Programme) were conducted in 2010 to address when and why physicians prescribe combination treatment:

- InforMed Insight conducted 75-minute interviews with 80 neurologists and geriatricians in 5 European countries. When physicians were asked for their criteria for initiating combination treatment, they stated that although MMSE scores were taken into account, they had less relevance in the moderate stage than in the milder stages of the disease. For them, the main reasons for initiating combination treatment were progression of the disease to the moderate/severe stage, clear degradation of behavioural symptoms, or a request from the patient's family/carer because of concern regarding patient decline. When asked why they prescribed combination treatment, the physicians stated that the reason was based both on the published evidence and on their own and their colleagues' clinical experiences. For them, the main treatment goals with combination treatment were to stabilise the patient, in terms of slowing the progression and preserving the function of the patient as much as possible, and to lessen the impact of the condition on the carers'/families' quality of life, especially in relation to behavioural aspects of the disease.
- The Adelphi Real World Disease Specific Programme (ARW DSP) collected prospective, quantitative and qualitative data from 552 general practitioners and specialists in 5 European countries. Physicians stated that the four main reasons for prescribing combination treatment were, in order of importance: slowing disease progression, delaying entry into care/nursing home, improving short-term memory, and improving/maintaining concentration/attention. A further reason for choosing combination treatment over AChEI monotherapy was the reduction in anxiety and reduction in irritability.

Data of a Decision Base market research survey were also provided. Results showed that the neurologists regarded combination treatment to be the most efficacious therapeutic approach available to treat moderate to severe AD. The arguments included effects on cognitive decline, function, behaviour, and global impression of change, all of which represent the clinical outcomes often used in studies of treatments for AD.

2.5.6.3. ***Review on epidemiological, market research and prescription data***

Epidemiological data

An overview of epidemiological studies including patients on memantine and AChEI combination treatment was provided including data from the following European countries: France, Spain, and the Czech Republic, Germany, Greece, Austria.

According to the applicant, trends for the global prevalence of memantine/donepezil combination treatment were globally similar to those observed for treatment with memantine and any AChEIs. Highest rates of this combination therapy were observed in France (45-47%), Spain (16- 38%); and the Czech Republic (9%). These rates were reduced relative to the overall prevalence of memantine/AChEI treatment as this category included patients treated with various other AChEIs in addition to donepezil. Based on this analysis, a calculation of the prevalence of donepezil prescriptions could be made up between 42% and 57% of total AChEI/memantine prescriptions. The prevalence of memantine/donepezil treatment was comparable between the overall AD population and the targeted indication (moderate to moderately severe AD). Within this subset of patients, donepezil was estimated to account for about half of total AChEI usage, being responsible for between 36% and 59% of AChEI prescriptions.

Market Research data

ARW-DSP

The ARW DSP was conducted in 2004, 2006, 2008 and 2010, in five European countries: United Kingdom, France, Germany, Spain and Italy. The study was conducted every 2 years (referred to as a 'wave'). Approximately 90 to 120 physicians (both general practitioners (GPs) and specialists including psychogeriatricians, geriatricians, psychiatrists, neuropsychiatrists, and neurologists) were recruited for each wave of the study. Physicians were asked to recruit their next 10 consecutive patients seen in consultation who met the following inclusion criteria: aged over 50 years and with symptoms of cognitive impairment. Patients with AD formed a subset of this sample.

Overall results are presented in Figures 9 and 10.

Figure 9

Figure 2. Proportions of memantine-treated patients with AD receiving mono- or combination therapy with any AChEI. Data from 2010 (ARW DSP).

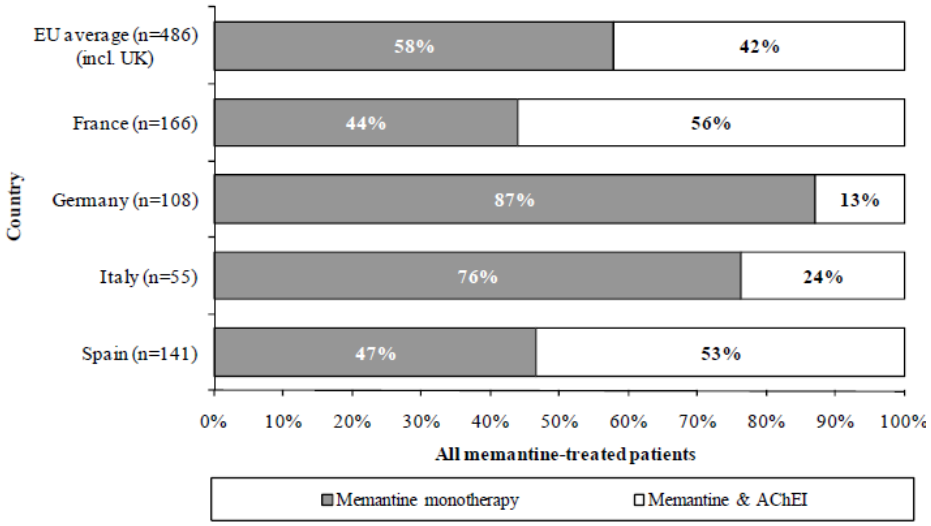
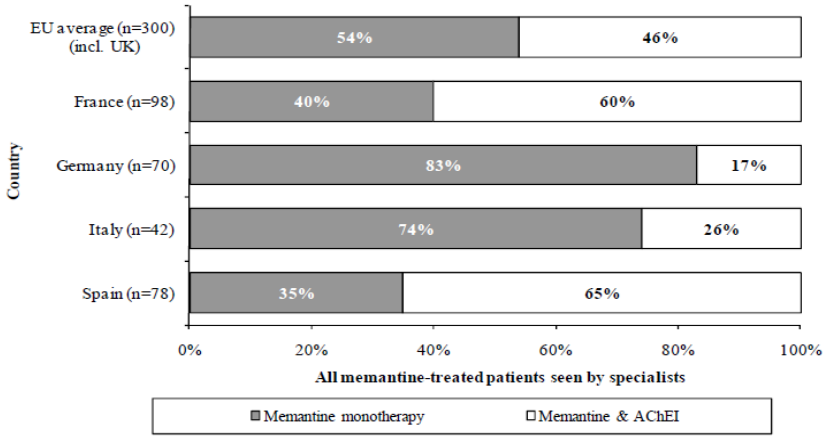


Figure 10

Figure 4. Proportions of memantine-treated patients with AD receiving mono- or combination therapy with any AChEI – Specialist Data from 2010 (ARW DSP).

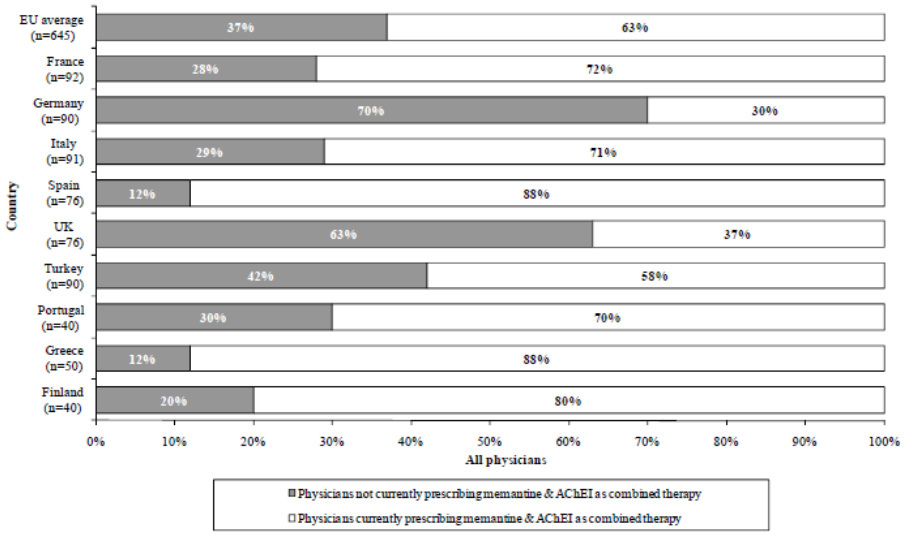


Cegedim Customer Information Online Tracker (CCI-OT)

Cegedim Customer Information carried out an online survey in May 2010 which targeted physicians (neurologists, psychiatrists, geriatricians, internal medicine and GPs) from nine countries in order to track sales force and marketing effectiveness. Recruited physicians (n = 645) completed a 10 minute online questionnaire which addressed their perceptions of different treatments available for AD and their prescription behaviour/habits (Figure 11).

Figure 11

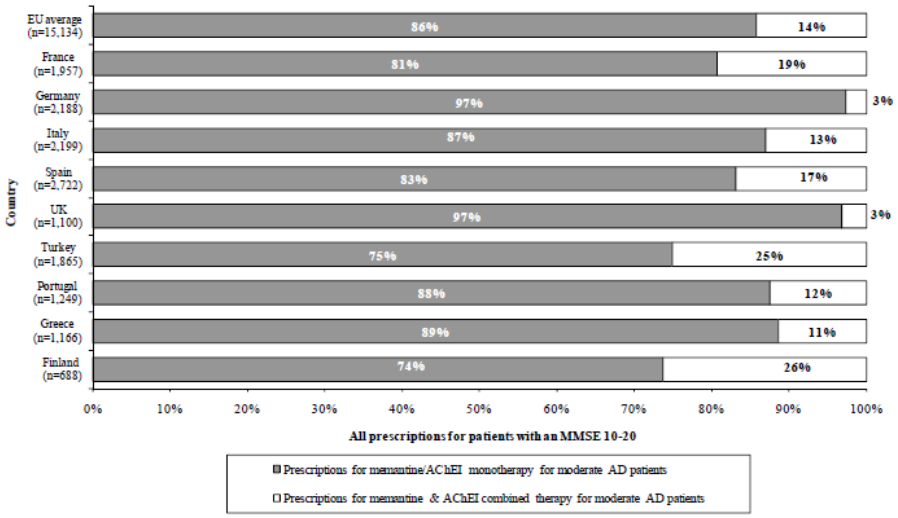
Figure 5. Proportions of physicians who prescribe memantine and AChEIs as combination therapy for patients with AD. Data from May 2010 (CCI-OT).



Physicians surveyed in the CCI-OT were also asked about the proportion of prescriptions that combined therapy would account for, out of all prescriptions for patients with moderate stage AD. Results varied by individual countries from 3% to 26%; however similar patterns in terms of which countries were typically reported to be either higher or lower prescribers of combination therapy, were recorded (see Figure 12).

Figure 12

Figure 9. Proportions of all prescriptions made for patients with moderate to moderately severe AD receiving combination therapy with memantine and AChEI. Data from May 2010 (CCI-OT).



c) *Decision Resources Physician Survey*

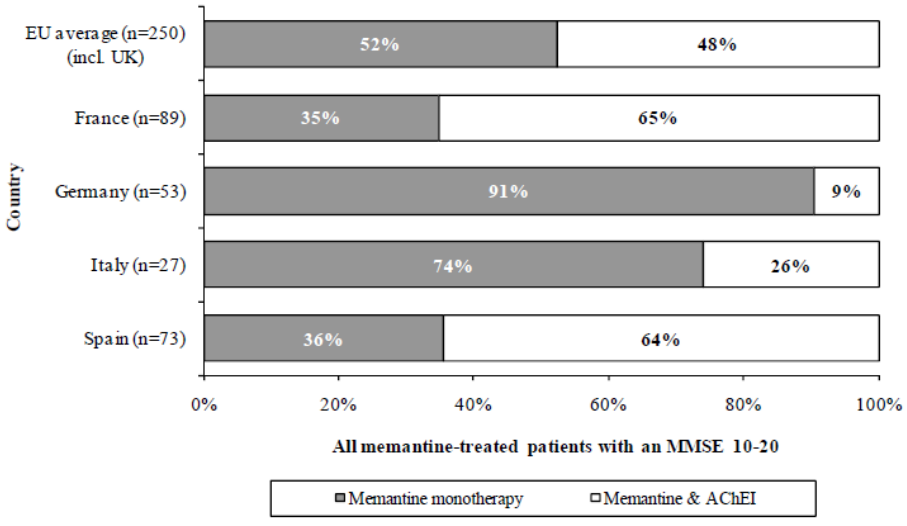
Decision Resources conducted market research during September 2009 in France (FR), Germany (DE), Italy (IT), Spain (ES) and United Kingdom (UK). A total of 256 neurologists (FR: 52; DE: 54; IT, ES, UK: 50) completed the survey over the internet. The survey was perception-based and assessed physician opinions in relation to different treatments available for AD.

Physicians were asked what proportion of their moderate stage patients would be receiving an AChEI alone versus an AChEI in combination with memantine. Responses ranged from 18% to 41%.

Data from ARW DSP showed the reported proportion of moderate to moderately-severe AD patients receiving memantine and an AChEI as combined therapy (see Figure 13).

Figure 13

Figure 7. Proportions of memantine-treated patients with moderate to moderately-severe AD receiving mono- or combination therapy with any AChEI. Data from 2010 (ARW DSP)



d) *Observational retrospective market research study*

Between December 2010 and January 2011, an observational market research study was conducted using retrospective analysis of the medical records of patients with AD. The primary objective of this study was to document the extent of use of combination therapy with donepezil in patients prescribed memantine across 15 countries in the EU (Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovakia, Spain, Sweden, United Kingdom).

Overall, 502 specialists (neurologists, geriatricians and psychiatrists) were recruited, who provided data for a total of 5,020 patients. The specialists agreed to retrieve patient records for the last 10 patients with AD that they had seen and to complete a questionnaire about themselves and their treatment practices. Results were summarised as follows:

- In this population, patients with moderate to moderately severe AD represented 51.1% of all patients and 55.4% of patients treated with AD drugs (treated patients).
- 55.2% of the patients who were prescribed memantine, and 58.4% of the patients with moderate to moderately severe AD who were prescribed memantine, received combination therapy with an AChEI.
- The AChEI most commonly used in combination with memantine was donepezil, which was used in 49.1% of all patients prescribed combination therapy and in 27.1% of all patients prescribed memantine.
- Donepezil was co-prescribed in 29.9% of all patients with moderate to moderately severe AD who were prescribed memantine.
- Of those patients receiving combination therapy with memantine plus donepezil: 52.8% were prescribed 20 mg of memantine; 83.4% were prescribed 10 mg of donepezil; 46.7% were prescribed 20 mg of memantine and 10 mg of donepezil.

Prescription Data

A report on prescription data was submitted. The objective was to investigate the extent of the co-prescription of memantine with AChEIs in general and, with donepezil, specifically, across a number of European countries. Results were drawn from 2 databases and are presented below.

a) IMS-Prescribing Insights Database (IMS-PID)

The IMS-PID was used to provide prescription estimates of memantine in combination with an AChEI for France, Germany, Italy, Spain and the United Kingdom (UK) from the period of April 2008 to April 2009. Results are presented in Figures 14 and 15.

Figure 14

Figure 2. Proportions of memantine-treated patients receiving mono- or combination therapy with any AChEI in 5 European countries (IMS-PID 2008/2009)

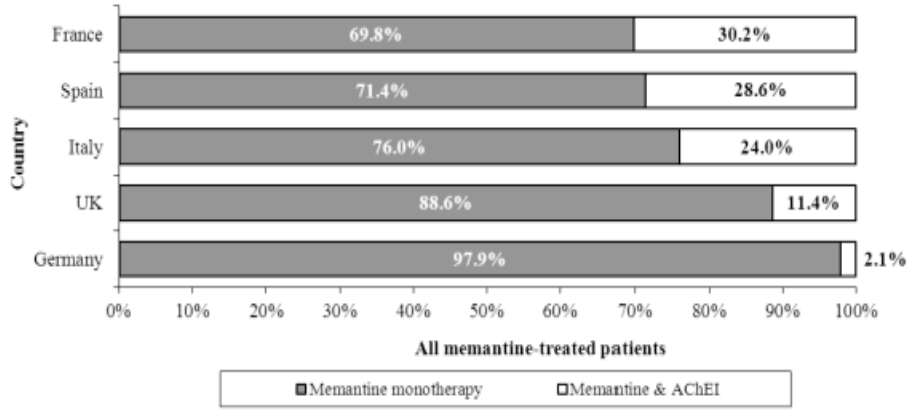
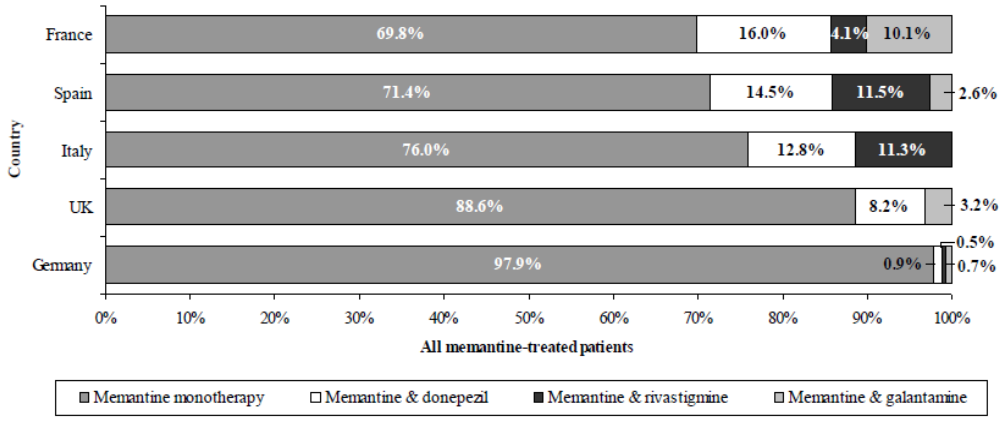


Figure 15

Figure 5. Proportions of all memantine-treated patients receiving mono- or combination therapy with donepezil versus other AChEIs (IMS-PID 2008/2009)



b) Cegedim Strategic Data-Longitudinal Patient Database (CSD-LPD)

The data in the CSD-LPD were considered observational, in that each interaction between a physician and patient was captured. The CSD-LPD contains data for France, Germany, Italy, Spain, UK and Belgium. Data from July 2009 to July 2010 were analysed. Detailed of the results are presented in Figures 16 and 17.

Figure 16

Figure 3. Proportions of memantine-treated patients receiving mono- or combination therapy with any AChEI in 6 European countries (CSD-LPD 2009/2010)

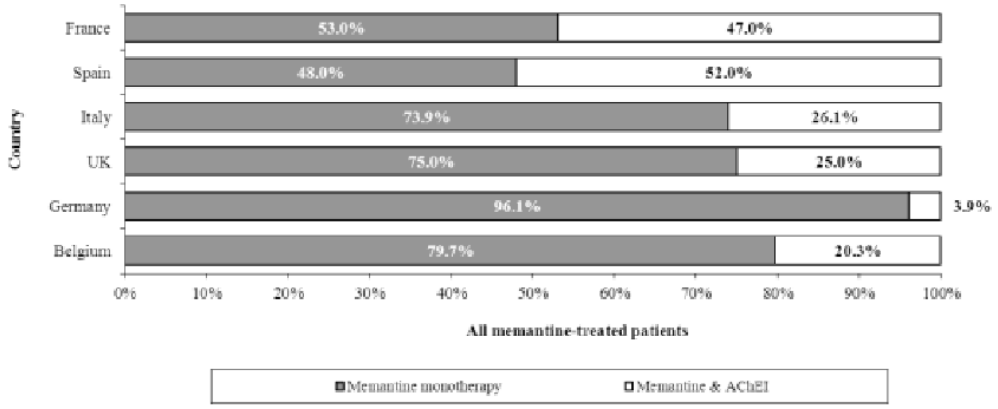
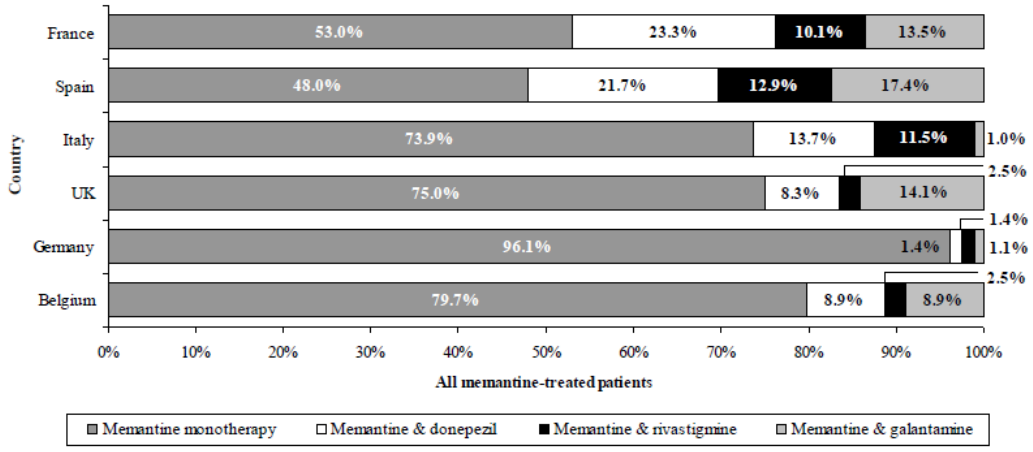


Figure 17

Figure 6. Proportions of memantine-treated patients receiving mono- or combination therapy with donepezil versus other AChEIs (CSD-LPD 2009/2010)



2.5.6.4. *Publication from Howard et al. – DOMINO study*

The DOMINO study included AD patients who were already treated with donepezil. Patients were randomly assigned to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine.

The 2 primary efficacy parameters were based on the standardised MMSE (SMMSE) score and the Bristol Activities of Daily Living Scale (BALDS). Results are presented in Figure 18.

Figure 18

Panel 5: Mean Scores on the Standardized Mini-Mental-State Examination and the Bristol Activities of Daily Living Scale; Panel taken from the publication Howard et al. [Howard 2012]

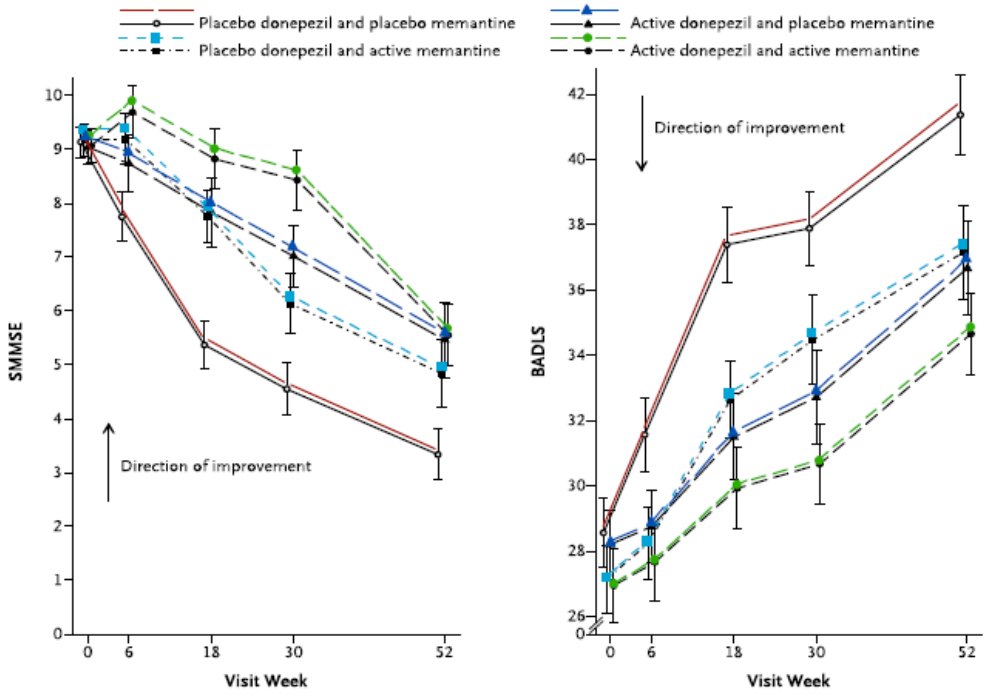


Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

For easier visualisation, colours were added to the lines indicating the individual treatment groups.

According to the applicant, the treatment effects obtained in the active treatment groups (combination therapy and monotherapy treatment arms) can be easily distinguished from the placebo group. Numerically, the best treatment effects for both primary efficacy parameters (SMMSE and BADLS) were consistently achieved in the combination treatment group. This was most prominent after 30 weeks of treatment and was still present at the end of the study (Week 52). At Week 52 approximately 60% of the patients initially included in the study were no longer participating, leading to a substantially reduced statistical power of the evaluations at Week 52. Furthermore, due to the different discontinuation rates of patients per treatment group, the size of treatment groups at Week 52 was no longer proportionate.

Efficacy of the combination over memantine alone

Following the CHMP reference to a recent publication from Howard et al. (2012) on the DOMINO study, the applicant further discussed the efficacy of the combination versus memantine. Of note, the same group of authors also previously published a paper on the Minimally Clinically Important Difference (MCID) for both primary efficacy parameters [Howard 2011]. For SMMSE score a 1.4 point difference was considered, whereas for BADLS score, a difference of at least 3.5 was found to be clinically important. According to the applicant, the results showed that combination treatment was superior to memantine monotherapy and, for this comparison, the pre-defined MCID was exceeded at Week 30 for both primary efficacy parameters SMMSE (MCID ≥ 1.4) and BADLS (MCID ≥ 3.5). Results at week 30 are presented in Table 18.

Table 18

Panel 6: Treatment Differences in SMMSE and BADLS Changes at Week 30

Comparison between the treatment groups at Week 30	MMSE		BADLS	
	Mean values	Difference between the treatment groups	Mean values	Difference between the treatment groups
Combination compared with Memantine	8.4; 6.1	2.3	30.7; 34.5	-3.8

The numbers above are derived form the Figure 3 (Panel_5 in this document) in the article Howard et al, 2012 (DOMINO study).

2.5.7. Discussion on clinical efficacy

The clinical efficacy data provided considered the CHMP Guideline on the Clinical Development of Fixed Medicinal Products (CPMP/EWP/240/95, Rev 1).

Clinical Efficacy

Study MEM-MD-02 showed that patients on memantine/donepezil treatment achieved better scores in cognitive scales and in daily living activities than patients continuing on donepezil at 24 weeks. In this study, the two primary endpoints were the changes from baseline at week 24 of the SIB total score and the ADCS-ADL modified score, and the secondary endpoints included the CIBIC- plus score. At week 24 (LOCF), the mean changes were : 2.5 and 0.9 for SIB total score and -3.4 and 2.0 for ADCS-ADL modified score for the placebo/donepezil and memantine/donepezil groups, respectively (BIS total score: $p<0.001$; ADCS-ADL modified score: $p=0.028$). For the CIBIC-plus score, the mean value was 4.66 for the placebo/donepezil group as compared to 4.41 for the memantine/donepezil group ($p=0.027$). Results from LOCF and OC analyses were consistent for these endpoints.

However, the contribution to the effect from memantine alone cannot be determined due to the lack of memantine monotherapy control arm. In addition, study MEM-MD-02 was not specifically designed for the proposed fixed-association dose. Hence, the CHMP considered that the study design for MEM-MD-02 did not allow to confirm the efficacy of the fixed combination in the intended population.

There were two other 24 week duration studies (MEM-MD-12, 10158). These studies recruited a low proportion of patients on donepezil and failed on their primary analysis to show statistical difference of the memantine/AchEI group compared to the placebo/AchEI group.

Other studies did not bring additional evidence, as none of them met their main efficacy endpoints, and as they varied in their design.

No specific dose-finding studies have been performed hence the optimum doses for the combination is currently unknown. The applicant justified this lack of studies based on the proposed indication for the fixed combination (substitution indication in patients already at stable doses of memantine 20 mg and donepezil 10 mg). Taking into account the continuous need for dose titration in AD patients, the CHMP was of the opinion that in accordance with the CHMP Guideline on the Clinical Development of Fixed Medicinal Products (CPMP/EWP/240/95, Rev 1) referred previously, dose response of the combination should have been investigated to determine to what extent each active component independently contributes to the efficacy and safety of the combination (see section 2.6).

Additional efficacy analyses

Efficacy of the combination over donepezil alone

Two meta-analyses were performed in the targeted population (moderate to moderately severe AD defined as patients with MMSE 10 to 19) treated with 20 mg memantine/10 mg donepezil (per day).

In the second meta-analysis including the largest number of trials, a total of 527 patients were included and represented a subpopulation (from 23.4% to 48.6%) of the total patients originally studied. According to the applicant, results in the three main efficacy domains (cognition, global assessment, and activities of daily living) were consistently in favour of the combination treatment compared with donepezil monotherapy in the first analysis. In addition, patients receiving donepezil/memantine treatment performed significantly better than patients treated with placebo/donepezil on cognition scales (LOCF) and global assessment (OC and LOCF) at Week 24, with a trend favouring the memantine/donepezil group in the LOCF analysis (p=0.09) for the domain activities of daily living.

A non-responder analysis was also performed in the targeted population to evaluate the efficacy of the combination on the reduction of clinical worsening. Non-responders were defined as a worsening in cognition (by at least 4 points in ADAS-cog, 5 points in SIB or 1 point in BGP-cog and any worsening in global assessment (ADCS-CGI-C/CIBIC-Plus) and any worsening in activities of daily living (ADL23, ADL19, BGP-care dependency) at study endpoint compared with baseline at week 24 . According to the applicant, statistical significant difference was observed for the donepezil/memantine group compared to placebo/donepezil group on the reduction of clinical worsening. Twice as many patients treated with placebo/donepezil experienced a marked clinical worsening in the three domains compared with patients treated with donepezil/memantine (LOCF 16.08% versus 8.53%, and OC 13.74% versus 7.73%).

Although these analyses seemed to suggest an additional effect of memantine when compared to donepezil alone, the CHMP was of the opinion that these results could only be considered as exploratory due to several limitations in their designs (e.g. examination of subgroup of patients, post hoc nature of the analyses, different efficacy endpoints assessed in each trial).

Efficacy of the combination over memantine alone

No additional analyses were initially provided by the applicant to address the concern over the lack of comparison of the efficacy of the combination versus memantine group on the basis that this application relates to a substitution indication.

However, during the evaluation, a recent publication from Howard et al. (2012) evaluating different therapeutic strategies in patients with moderate to severe AD (DOMINO study) was identified by the CHMP. In this study, patients already treated with donepezil were randomly assigned to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. After 52 weeks of follow-up there was no significant benefit of adding memantine to donepezil with respect to scores on cognition (MMSE 0.8 points higher with memantine than with placebo; 95% CI, −0.1 to 1.6; p=0.07) or on the activities of daily living (BADLS 0.5 points lower with memantine than with placebo; 95% CI, −2.2 to 1.2; p= 0.57). From the CHMP viewpoint, these data reinforce the uncertainties over the efficacy of the combination and its place in AD therapy. These uncertainties further question its use as substitution indication in the treatment of AD in the absence of robust data demonstrating the efficacy of the combination in the intended population.

According to the applicant, the treatment effects obtained in the active treatment groups (combination therapy and monotherapy treatment arms can be easily distinguished from the placebo group. Numerically, the best treatment effects for both primary efficacy parameters (SMMSE and BADLS) were consistently achieved in the combination treatment group. This was most prominent after 30 weeks of treatment and was still present at the end of the study (Week 52). Therefore, it was the applicant's opinion that the results obtained at Week 30 should be considered as a more reliable basis

for making conclusions regarding combination treatment than results obtained at Week 52. The acceptability of the proposed analysis was however questioned by the CHMP due to several methodological limitations. Indeed, this was a post-hoc analysis with its inherent limitations but also in the absence of the numbers for the mean values, estimations were made by the applicant. In addition the time-point of week 30 was chosen arbitrarily without justification. The DOMINO study included a more severe population (MMSE 5-13) than the targeted indication applied for ie moderate to moderately severe AD (MMSE 10-19).

In the absence of robust data demonstrating the efficacy of the combination in the intended population, the CHMP considered these results of limited relevance. Moreover, the CHMP noted that the 60 % drop out rates at week 52 could also reflect the absence of a real temporal benefit in the use of the fixed combination in most patients that are on combination therapy since the patients did not stay on the highest dose of both memantine/donepezil for a long period, and that most likely a detitration of either component was required.

Data on simultaneous use

Treatment guideline/expert panel recommendations on management of AD vary across European Union. Seventeen references to European guidelines have been provided. According to the Applicant, the majority of the guidelines acknowledged the combination use in the moderate stage of the disease. The CHMP however noted that 2 recent European publications ie "NICE technology appraisal guidance 217: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease" and "EFNS Guidelines for the diagnosis and management of Alzheimer's disease, 2010" stated that the benefits of adding memantine to AChE inhibitors were not clear with the currently available data. Moreover, the conclusions of the NICE review were that *"combination treatment with memantine and AChE inhibitors could not be recommended because of lack of evidence of additional clinical efficacy compared with memantine monotherapy*" suggesting that the available data on simultaneous use are currently insufficient to support a substitution indication for a fixed combination in the indication applied for (moderate to moderately severe AD).

Published studies related to 6 clinical trials (including MEM-MD-02 and MEM-MD-12, previously discussed) and 2 observational studies. Considering the lack of control arm including memantine alone in the clinical trials and the methodological limitation inherent to observational design, the CHMP considered that no new relevant information could be retrieved from these publications.

Results from the epidemiological studies showed important differences in the use of the combination among the European countries. According to the applicant, these differences could be explained by the different reimbursement policy across the EU. However, the CHMP considered that these differences also reflected the general lack of consensus regarding the clinical use of the combination in the EU. Data were made available for 6 European countries only, thus not allowing a generalisation of the findings to the EU population. Market research and prescription data also revealed considerable differences in estimates of the use and prescription of memantine in combination with AChEIs (including donepezil) across the EU (see section 2.5.6.3).

In view the above, the CHMP considered that whilst the presented bibliographical analysis had some methodological limitations (e.g. retrospective access to the data, lack of randomization, limited number of countries or patient population involved), memantine and AChEIs (mostly donepezil) were being prescribed as a combination therapy for AD. However, their clinical use varied considerably across the EU. The differences could be explained by the limited efficacy of available treatments for the treatment of AD, the lack of consensus in the therapeutic recommendations in force in each country, the differences in the financial supplies of medicines or in the local organization of health systems. These findings also indirectly correlated with the heterogeneity seen among available treatment

guidelines/expert panel recommendations previously referred to. The CHMP was therefore of the opinion that the data on simultaneous use of memantine 20 mg and donepezil 10 mg across the European Union were insufficient to support a substitution indication for the fixed combination in the treatment of moderate to moderately severe Alzheimer disease.

During the oral explanation, the applicant claimed that the requirements outlined in the CHMP guideline on the clinical development of fixed medicinal product (CPMP/EWP/240/95) were met for this application, and reiterated their position on the widespread use of the combination being adequately established. In addition, the applicant referred to the DOMINO study and the additional post-hoc analyses performed to further substantiate the efficacy of the combination in the intended population.

Having considered the oral explanation given by the applicant, the CHMP maintained its position that the efficacy of the combination has not been sufficiently demonstrated since the presented data did not change the overall efficacy discussion.

2.5.8. Conclusions on the clinical efficacy

The CHMP concluded the following:

- The efficacy of the combination (memantine 20 mg/donepezil 10 mg) versus the components administered individually in the treatment of moderate to moderately severe Alzheimer's disease has not been sufficiently demonstrated

- The data on simultaneous use of memantine 20 mg and donepezil 10 mg across the European Union are insufficient to support a substitution indication for the fixed combination in the treatment of moderate to moderately severe Alzheimer's disease.

2.6. Clinical safety

From the safety database including 24 clinical studies, 5 pools of studies were made according to the design of the studies as follows: 1) 24-week, Double-blind, Placebo-controlled Studies (MEM-MD-02, MEM-MD- 12, MEM-MD-22, and 10158) or pool 1; 2) 12-week, Double-blind, Placebo-controlled Studies Pool (MEM-MD-23 and MEM-MD-71) or pool 2; 3) 24-28-week, Open-label Extension (OLEX1) Studies (MEM-MD-03AB, MEM-MD-12A, and 10252) or pool 3; 4) 52-week, Open-label Extension (OLEX2) Studies (MEM-MD-03C and MEMMD-12B) or pool 4; 5) 12-week, Open-label Studies (MRZ 0608 and MRZ 3001) or pool 5.

Pools 3, 4 and 5 included extension studies that were not submitted as part of this application to support the efficacy.

2.6.1. Patient exposure

A total of 1626 patients received memantine/donepezil (MEM/DPZ) and accrued 1522.7 patient years of exposure to memantine in combination with donepezil during the studies. Overall, nearly 75% of the patients received 10 mg/day donepezil, 24% received 5 mg/day donepezil, and less than 1.5% received another dose.

Twenty % of the overall patients had severe AD (MMSE<10), two-thirds had moderate AD (MMSE>=10 AND >=19), AND 10% had mild AD (MMSE>19). Approximately two-thirds of these patients were women and had a mean age at inclusion of 75 years. The vast majority (more than 90%) were Caucasian. The prevalence of concomitant diseases and coadministered medication were similar

between patients in memantine/donepezil versus those treated with placebo/donepezil. No relevant differences were observed between both groups of patients.

In pool 1, the exposures to donepezil accrued prior to study start were in the memantine/donepezil (MEM/DPZ) and placebo/donepezil (PBO/DPZ) groups: 1066 and 1071 patient years, respectively. The mean duration of donepezil treatment prior to study start was approximately 2 years and 3 months in both treatment groups.

Further details on duration of exposure by intervals are provided in Tables 19-21 for double blind placebo controlled studies, pools 1 and 2 and the study 10112, respectively.

Table 19

Table 2 Duration of Exposure to IMP by Intervals (APTS, DPZ): 24-week, DB, PBO-controlled Studies

	PBO/DPZ	MEM/DPZ	Total
Patients Treated	465	473	938
< 1 week n (%)	3 (0.6)	1 (0.2)	4 (0.4)
1 - 4 weeks n (%)	18 (3.9)	16 (3.4)	34 (3.6)
5 - 12 weeks n (%)	43 (9.2)	28 (5.9)	71 (7.6)
13 - 16 weeks n (%)	12 (2.6)	4 (0.8)	16 (1.7)
17 - 24 weeks n (%)	367 (78.9)	397 (83.9)	764 (81.4)
25 - 36 weeks n (%)	22 (4.7)	27 (5.7)	49 (5.2)

Table 20

Table 3 Duration of Exposure to IMP by Intervals (APTS, DPZ): 12-week, DB, PBO-controlled Studies

	PBO/DPZ	MEM/DPZ	Total
Patients Treated	53	61	114
1 - 4 weeks n (%)	1 (1.9)	0 (0.0)	1 (0.9)
5 - 12 weeks n (%)	35 (66.0)	39 (63.9)	74 (64.9)
13 - 16 weeks n (%)	17 (32.1)	22 (36.1)	39 (34.2)

Table 21

Table 4 Duration of Exposure to IMP by Intervals (APTS, DPZ): 52-week, DB, PBO-controlled Study 10112

	PBO/DPZ	MEM/DPZ	Total
Patients Treated	65	57	122
1 - 4 weeks n (%)	1 (1.5)	1 (1.8)	2 (1.6)
5 - 12 weeks n (%)	5 (7.7)	4 (7.0)	9 (7.4)
13 - 16 weeks n (%)	2 (3.1)	1 (1.8)	3 (2.5)
17 - 24 weeks n (%)	1 (1.5)	3 (5.3)	4 (3.3)
37 - 52 weeks n (%)	37 (56.9)	37 (64.9)	74 (60.7)
> 1 year n (%)	19 (29.2)	11 (19.3)	30 (24.6)

Note: IMP: investigational medicinal product; APTS: patients-treated Set or Safety Population comprised all patients who took at least one dose of investigational medicinal product ; APTS, DPZ: subset of patients from the APTS or Safety Population who received donepezil concomitantly with memantine or placebo.

Figures for the total number of patients were: 473 (pool 1), 61 (pool 2) and 57 (study 11012) for the group receiving MEM/DPZ and 465 (pool 1), 53 (pool 2) and 65 (study 11012). In the extension studies, a total of 675 patients received MEM/DPZ in pool 3 and 365 patients in pool 4.

2.6.2. Adverse events

Data are presented in Tables 22 and 23 for pools 1, 2 and study 10112. Data for extension studies are presented in Table 24 (pools 3 and 4 and study MEM-MD-03D).

Table 22

Panel 6 Adverse Events With an Incidence of 5% or More (APTS, DPZ): 12- and 24-week, Placebo-controlled Studies Pools

	24-week, Placebo-controlled Studies Pool				12-week, Placebo-controlled Studies Pool			
Preferred Term	PBO/DPZ		MEM/DPZ		PBO/DPZ		MEM/DPZ	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients Treated	465		473		53		61	
Patients with Adverse Events	359	(77.2)	369	(78.0)	27	(50.9)	36	(59.0)
Agitation	41	(8.8)	40	(8.5)	1	(1.9)	2	(3.3)
Fall	41	(8.8)	38	(8.0)	3	(5.7)	2	(3.3)
Confusional state	12	(2.6)	29	(6.1)**	0		3	(4.9)
Dizziness	31	(6.7)	28	(5.9)	0		2	(3.3)
Diarrhoea	37	(8.0)	26	(5.5)	5	(9.4)	4	(6.6)
Headache	17	(3.7)	26	(5.5)	0		0	
Upper respiratory tract infection	22	(4.7)	24	(5.1)	1	(1.9)	1	(1.6)
Urinary tract infection	31	(6.7)	21	(4.4)	2	(3.8)	2	(3.3)

** p <0.01
PBO: placebo; DPZ: donepezil; MEM: memantine
Cross-reference: Tables 55 and 61, Module 2.7.4, *Summary of Clinical Safety*

Table 23 Adverse Events With an Incidence of 5% or More (APTS, DPZ): study 10112

	PBO/DPZ		MEM/DPZ		
Preferred Term	n	(%)	n	(%)	p-value #
Patients Treated	65		57		
Patients with Adverse Events	42	(64.6)	35	(61.4)	
Fall	6	(9.2)	7	(12.3)	0.770
Headache	3	(4.6)	6	(10.5)	0.302
Confusional state	1	(1.5)	5	(8.8)	0.097
Agitation	0	(0.0)	4	(7.0)	0.045 *
Dizziness	2	(3.1)	4	(7.0)	0.416
Hypertension	0	(0.0)	4	(7.0)	0.045 *
Oedema peripheral	0	(0.0)	4	(7.0)	0.045 *
Prostatic specific antigen increased {gs}	0	(0.0)	1	(5.6)	0.467
Abdominal pain	0	(0.0)	3	(5.3)	0.099
Anxiety	2	(3.1)	3	(5.3)	0.664
Cough	2	(3.1)	3	(5.3)	0.664
Depression	0	(0.0)	3	(5.3)	0.099
Diarrhoea	8	(12.3)	3	(5.3)	0.216
Nasopharyngitis	1	(1.5)	3	(5.3)	0.339
Somnolence	1	(1.5)	3	(5.3)	0.339
Urinary tract infection	4	(6.2)	3	(5.3)	1.000
Weight increased	1	(1.5)	3	(5.3)	0.339
Urinary incontinence	5	(7.7)	2	(3.5)	0.447
Vomiting	4	(6.2)	2	(3.5)	0.684
Weight decreased	5	(7.7)	1	(1.8)	0.213
Benign prostatic hyperplasia {gs}	2	(6.7)	0	(0.0)	0.498

Coding is done in MedDRA version 13.1
Fisher^s Exact Test, 2-tailed
* = p< 0.05 ** = p < 0.01 *** = p < 0.001

Final Combo ST_AESG_DB_RT10112_I_5P 12APR2011:17:18:47 1001/001 - TFL/SAD Build Numbers

Cross-reference: Table 65, Module 2.7.4, *Summary of Clinical Safety*

Table 24

Panel 8 Adverse Events With an Incidence of 5% or More (APTS, DPZ): Open-label Extension Studies

	24-28-week, $OLEX_1$ Studies Pool				52-week, $OLEX_2$ Studies Pool		54-week, OLEX Study MEM-MD-03D	
Preferred Term	**PBO/DPZ[a]**		**MEM/DPZ[a]**		**MEM/DPZ**		**MEM/DPZ**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients Treated	324		351		365		119	
Patients with Adverse Events	227	(70.1)	253	(72.1)	266	(72.9)	92	(77.3)
Agitation	23	(7.1)	27	(7.7)	41	(11.2)	14	(11.8)
Fall	26	(8.0)	23	(6.6)	38	(10.4)	11	(9.2)
Urinary tract infection	25	(7.7)	16	(4.6)	24	(6.6)	14	(11.8)
Dizziness	21	(6.5)	18	(5.1)	12	(3.3)	0	
Dementia Alzheimer's type	1	(0.3)	5	(1.4)	6	(1.6)	7	(5.9)
Prostatomegaly (gs)	0		2	(1.4)	2	(1.4)	2	(5.9)
Pneumonia	5	(1.5)	3	(0.9)	16	(4.4)	6	(5.0)

PBO: placebo; DPZ: donepezil; MEM: memantine; gs: gender specific
Cross-reference: Tables 70, 78, and 82, Module 2.7.4, *Summary of Clinical Safety*

a Lead-in treatment group

2.6.3. Serious adverse event / deaths / other significant events

Serious adverse events (SAE)

In pool 1, the incidence of SAEs was 12% in the MEM/DPZ group and 11% in the PBO/DPZ group. During long-term treatment, there was a tendency that incidence of SAEs increased with the study duration: 13%, 22% and 35% respectively in pools 3 (24-28 weeks), 4 (52 weeks) and in 54 week study MEM-MD-03D.

In pool 1, SAEs that occurred with an incidence of 1% or more in either treatment group were fall (MEM/DPZ: 1%, n=7, 2 rib fracture; PBO/DPZ: 1%, n=6, 3 hip fracture]), hip fracture (MEM/DPZ: 1% [n=3]; PBO/DPZ: 1% [n=5]) ; agitation (MEM/DPZ: 1%, n=7 ; PBO/DPZ: <1%, n=2). In pool 2, fall was reported as SAEs in more than 1 patient in either treatment group (MEM/DPZ: 2%, n=1; PBO/DPZ: 4%, n=2) as well as ankle fracture (MEM/DPZ: none; PBO/DPZ: 4% , n=2).

In the extension studies, additional types of SAEs occurred with an incidence of 1% or more and were as follows: syncope (MEM/DPZ: 1%, n=2 ; PBO/DPZ: 1%, n=4), dehydration (MEM/DPZ: <1%, n=1; PBO/DPZ: 1%, n=4), prostate cancer (MEM/DPZ: none; PBO/DPZ: 2%, n=2), dementia Alzheimer's type (4%, n=5). Pneumonia was reported as SAEs occurring in 10 or more patients (3%) in pool 4 ; dementia Alzheimer's type (4%, n=5), agitation (3%, n=4) and urinary tract infection (3%, n=4) were reported as SAEs occurring in 4 or more patients in study MEM-MD-03D.

Deaths

A total of 80 patients died during treatment with MEM/DPZ or PBO/DPZ or within 30 days thereafter.

In pool 1, a total of 8 patients died during treatment with MEM/DPZ (n=3) or PBO/DPZ (n=5). All events except the cardiac failure in one patient, were considered not related to treatment by the investigator. In study 10112, 2 patients in the MEM/DPZ group died during the study. None of the events were considered related to treatment by the investigator. None the patients in the PBO/DPZ group died during the study.

In the extension studies, 58 deaths were reported. In pool 3, a total of 17 patients died, 6 patients who had received MEM/DPZ and 11 patients who had received PBO/DPZ in the lead-in studies. All events, with the exception of cardiac failure and failure in the PBO/DPZ group, were considered not related to treatment by the investigator. In pool 4, a total of 19 patients died . All events, with the exception of acute renal failure and 1 cerebrovascular accident, were considered not related to treatment by the investigator. In study MEM-MD-03D, a total of 14 patients (12%) died. The events were considered not related to treatment by the investigator in all patients, except in two of them (cardiac arrest and pulmonary embolism cases).

Other deaths were reported in studies MEM-MD-50 (n=2), MEM-MD-54 and MEM-MD-82 (n=10); MEM-MD-51 (n=6). For 3 patients, the events were considered related to treatment by the investigator (acute myocardial infarction, bundle branch block, and ventricular arrhythmia; cerebrovascular accident; and cardiorespiratory arrest).

Other significant events

Confusional state, agitation, fall and dizziness related events were considered as significant events and were further analysed. In this analysis, a statistical difference between the two treatment groups in the overall incidence of patients with confusional state was noted (pool 1: PBO/DZP, 3%, n=12 versus MEM/DZP, 6%, n=29, $p \leq 0.01$). This finding was considered driven mainly by differences in the titration period, indicating that confusional state may be associated with memantine treatment initiation. In pool 3 (24-28-week, open label extension studies), 7 patients in each of the lead-in treatment groups reported confusional state during the initial 4- week titration period. The events that occurred during long-term treatment with MEM/DPZ were evenly distributed over time.

2.6.4. Laboratory findings

No relevant safety findings were noted in terms of changes in vital signs or laboratory parameters to the exception of liver enzyme elevations, considered as a known risk with memantine treatment.

2.6.5. Safety in special populations

No data were initially provided to address the safety in special populations. At the CHMP request, the applicant provided safety subgroup analyses of patients with renal, hepatic impairment, concomitant diseases (including cardiovascular diseases, hypertension, diabetes, or psychiatric disorders) and of patients treated with selected concomitant medication at baseline.

In patients with renal impairment, a higher incidence of cardiac events was observed in the MEM/DZP group (6 patients, 15%) as compared with the PBO/DZP group which did not experience any cardiac events. In the MEM/DPZ group, 2 patients each experienced cardiac failure congestive and myocardial infarction. In addition, atrial fibrillation, bradycardia, supraventricular extrasystoles, supraventricular tachycardia, and tachycardia were reported for one patient each.

In patients with hepatic impairment, 8 of 10 patients in the placebo/donepezil group, compared with only one patient out of 5 in the memantine/donepezil group, experienced adverse events.
No relevant findings were observed across treatment groups in the subgroup analysis of patients with concomitant diseases. Higher incidence of vascular event was noted in patients treated with memantine/donepezil as compared to placebo/donepezil across the different subgroups analysed.

Gastrointestinal events were reported with a higher frequency in patients treated with memantine/donepezil than in patients treated with placebo/donepezil in the subgroup of patients who were treated concomitantly with anti-inflammatory anti-rheumatic agents and also in the targeted population (defined as patients with MMSE score 10-19 who are treated with 20 mg memantine/10 mg donepezil or placebo/10 mg donepezil per day).

The CHMP also noted the very broad criteria used for defining patients with renal or hepatic impairment which may hamper the comparison with the overall population as the specificity of the analysis become low.

2.6.6. Safety related to drug-drug interactions and other interactions

In study MEM-PK-07, there were no serious AEs reported. Twenty (83.3%) of the twenty-four subjects reported a total of 111 treatment emergent adverse events Ninety-eight (98) of the AEs occurred when subjects were receiving donepezil alone, 3 occurred following memantine alone, and 10 occurred following the co-administration of memantine and donepezil. The events were generally mild to moderate in severity. The most common AEs were headache, nausea, fatigue, weakness, dizziness, diarrhoea, vomiting, and lightheadedness.

2.6.7. Discontinuation due to adverse events

In pool 1, a total of 473 patients received MEM/DPZ and 465 patients received PBO/DPZ. The overall withdrawal rate was 14% in the MEM/DPZ group and 20% the PBO/DPZ group; 7% of the patients in the MEM/DPZ group and 11% of the patients in the PBO/DPZ group withdrew due to adverse events.

In pool 2, a total of 61 patients received MEM/DPZ and 53 patients received PBO/DPZ. The overall withdrawal rate was 5% in the MEM/DPZ group and 4% in the PBO/DPZ group; 3% of the patients in the MEM/DPZ group and 2% of the patients in the PBO/DPZ group withdrew due to adverse events. In study 11012, a total of 57 patients received MEM/DPZ and 65 patients received PBO/DPZ. The overall withdrawal rate was 26% in the MEM/DPZ group and 15% in the PBO/DPZ group; 14% of the patients in the MEM/DPZ group and 11% of the patients in the PBO/DPZ group withdrew due to adverse events.

In the extension studies, a total of 675 patients received MEM/DPZ in pool 3 and 365 patients in pool 4. The overall withdrawal rates were respectively 12% and 27%; 4% of the patients withdrew due to adverse events in pool 3 and 10% in pool 4. In a 54 week study (MEM-MD-03D), a total of 119 patients received MEM/DPZ. The overall withdrawal rate was 52%; 15% of the patients withdrew due to adverse events.

2.6.8. Post marketing experience

The presented data were mainly based on memantine postmarketing database since the applicant is not marketing donepezil and had therefore no access to the corresponding postmarketing database. The estimated cumulative patient exposure to memantine in clinical studies and postmarketing use was approximately 5.7 million patient years as of 31 December 2010. Up to 15 December 2010, the overall number of memantine monotherapy reports was 2859. A total of 22% of the spontaneous reports received for memantine are from patients who received concomitant donepezil. Overall, both substances were assessed as suspect drugs in 148 cases (104 serious and 44 non-serious), and memantine was assessed as suspect and donepezil as concomitant drug in 701 cases (367 serious and 334 non-serious).

The most frequently (≥2%) reported serious reactions when both drugs were assessed as suspect: were fall (4.7%), convulsion (3.8%), confusional state (2.9%), somnolence (2.4%), and tremor (2.1%). The most frequently (≥3%) reported non-serious reactions were fatigue (4.3%), nausea (4.3%), dizziness (4.3%), diarrhoea (3.2%), decreased appetite (3.2%), confusional state (3.2%), and urinary incontinence (3.2%).

The most frequently (≥2%) reported serious reactions when memantine was assessed as suspect and donepezil as concomitant were: fall (3.7%), convulsion (2.6%), and urinary tract infection (2.0%).

The most frequently (≥2%) reported non-serious reactions were confusional state (6.6%), agitation (5.3%), dizziness (4.3%), gait disturbance (2.5%), fatigue (2.4%), fall (2.1%), aggression (2.1%).

In an analysis of 2859 spontaneous cases involving memantine as monotherapy, the most frequently reported events were confusional state (3.6%), agitation (2.9%), somnolence (2.7%), dizziness (2.6%), aggression (2.0%), fall (2.0%), and convulsion (2.0%).

2.6.9. Discussion on clinical safety

A total of 1627 patients (in the entire range of AD) have been exposed to memantine in combination with DPZ. The size of the safety database as well as the short (24 weeks) and long term (52 weeks) exposure to the combination were considered sufficient and adequate to characterise the safety profile of the combination (memantine 20 mg/donepezil 10 mg). Safety population was predominantly formed by Caucasian females with a median age of 75 years of age and sufficiently representative of the targeted indication. Patient retention in the studies ranged from 95% (12 weeks) to 50% (54 weeks), the withdrawal rates being proportional to the study duration. The number of patients discontinuing due to adverse events did not differ significantly between memantine and placebo groups.

The most frequently reported AEs in the subjects receiving MEM/DPZ included agitation, fall, confusional state, dizziness, diarrhoea, headache, upper respiratory tract infection and urinary tract infection. Many of the most common AEs were known to be commonly associated with AD (confusion, agitation, depression). Other AEs less likely to be disease related were nausea, vomiting and diarrhoea. The majority of AEs was of mild to moderate intensity and did not lead to discontinuation of study medication. The overall incidences of AEs were similar in the MEM/DPZ and PBO/DPZ groups in the short-term exposure, except for confusional state and headache that were more frequent in the combination group. The incidence of most of AEs reported with MEM/DPZ increased with the exposure. Unlike donepezil monotherapy group (in which AEs rates decreased over time), patients treated with the combined therapy showed significantly higher incidence of nervous, digestive and urinary tract disturbances in long term treatment.

Overall, the CHMP considered that the lack of comparison with a treatment group including memantine alone did not allow to conclude on these safety findings and that the present safety analysis was uncomplete.

A total of 80 patients died during treatment with MEM/DPZ or PBO/DPZ or within 30 days thereafter. In the clinical trials most of deaths were not related to the treatment. In general, mortality rates in both groups were similar and deaths related to treatment were low. There were no obvious differences between the groups. Most of serious adverse events were related to cardiovascular, respiratory and infections disorders and did not appear to show a specific pattern. Dehydration, syncope and pneumonia cases were reported in the studies.

The overall incidence of the serious adverse events was similar between both treatment groups. The majority of SAEs were assessed as unrelated to study medication and SAEs increased with duration of the study. Fall and fractures are the most common SAEs. The incidence of fall (serious or non-serious) was similar between the MEM/DPZ and PBO/DPZ groups in the placebo-controlled studies.

Apart from the elevation of liver enzymes, no relevant findings were noted in terms of changes in vital signs or laboratory parameters. Although, this safety concern is already existing for memantine, it is uncertain to what extent the combination with donepezil represents a potential increased risk with respect to the monotherapy in the absence of comparison.

Postmarketing data suggested an increased risk of fall, convulsion and tremor for the combination as compared to memantine.

Additional analyses

At the CHMP request, the applicant provided additional analyses aiming at comparing the safety profile of the combination versus memantine alone. These analyses were of qualitative nature and compared safety findings from 4 randomised, double-blind, placebo-controlled studies with memantine monotherapy (MEM-MD-01, MEM-MD-10, MRZ 90001-9605, 99679). MEM-MD-10 and 99679 evaluated the efficacy and safety of memantine in patients with mild to moderate AD, whereas MEM-MD-01 and MRZ 90001-9605 evaluated the efficacy and safety of memantine in patients with moderate to severe AD. Therefore, additional comparisons were made between patients with similar AD severities (mild to moderate or moderate to severe) who have been treated with the memantine/donepezil combination or with memantine monotherapy.

This qualitative comparison did not reveal any new relevant safety findings. The AE profile appeared to be comparable between the combination and memantine group. However, among moderate to severe AD patients, the incidence of confusion and fall in patients with the combination was higher than in patients with memantine monotherapy (confusion : 8% in MEM-MD-02 versus 5% in MEM-MD-01 and 3% in 90001-9605, fall: 7.4% in MEM-MD-02 versus 5.6% in MEM-MD-01 and 7% in 90001-9605).

2.6.10. Conclusions on the clinical safety

No new relevant safety findings were noted. The CHMP concluded that the safety profile of the combination (memantine/donepezil) was adequately characterised, considering the AE profiles of the individual components.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Acrescent is a fixed-dose combination (FDC) product of memantine (20 mg) and donepezil (10 mg), presented as film-coated tablets (memantine 20 mg/donepezil 10 mg). Acrescent has been developed as a substitution indication i.e. in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets. This simplification of therapy by decreasing the number of individual dose units to be taken by the patient, may improve patient compliance and was therefore considered as a potential therapeutic advantage to support the present application.

As a general statement, a substitution indication would be acceptable in case of drugs with a wide therapeutic experience and an adequately established benefit/risk ratio. There are several examples of accepted fixed combinations in therapeutic areas like diabetes or hypertension. Those combinations have demonstrated to be efficacious and safe, improve patient adherence and they are widely recommended in treatment guidelines.

The main evidence presented to document the efficacy of the fixed dose combination came from study MEM-MD-02. This study evaluated the effects of memantine added to ongoing treatment with donepezil in patients with moderate to severe AD. Subjects on donepezil had been treated for more than 6 months before entry into the study at a stable dose (5-10 mg/day). In this study, results showed that patients on memantine/donepezil treatment achieved better scores in cognitive scales and in daily living activities than patients continuing on donepezil at 24 weeks. The two primary endpoints were the mean changes from baseline at week 24 of the SIB total score and the ADCS-ADL modified score and the secondary endpoint included the CIBIC- plus score. At week 24 (LOCF), the mean changes were : 2.5 and 0.9 for SIB total score and -3.4 and 2.0 for ADCS-ADL modified score for the placebo/donepezil and memantine/donepezil groups, respectively (SIB total score: $p<0.001$; ADCS-ADL modified score: $p=0.028$). For the CIBIC-plus score, the mean value was 4.66 for the placebo/donepezil group as compared to 4.41 for the memantine/donepezil group ($p=0.027$). Results from LOCF and OC analyses were consistent for these endpoints.

Uncertainty in the knowledge about the beneficial effects.

No specific dose-finding studies have been performed hence the optimum doses for the combination is currently unknown which is a concern in this setting due to continuous need for dose titration in AD patients. The DOMINO study showed that by week 52, 60% of patients had dropped out suggesting that patients did not stay on the highest dose of both memantine/donepezil for a long period, and that a detitration of either component was required.

In the presented clinical studies, only study MEM-MD-02 had statistically positive results. However, even in this study, the question on whether the achieved improvement is due to the effect of memantine could not be determined due to the lack of a control arm including memantine alone. In addition, study MEM-MD-02 was not specifically designed for the proposed fixed-association dose. Therefore, the design of this study did not allow to confirm the efficacy of the combination in the intended population.

In fact, none of the other studies showed statistical difference on their primary analyses. These studies were also lacking of memantine arm and used different primary endpoints. The majority of them were of small size small size and/or featured a low proportion of of subjects receiving donepezil.

Additional meta-analyses and non responder analysis performed by the applicant seemed to suggest an additional effect of memantine when compared to donepezil alone. However these results could only be considered as exploratory due to several limitations in their designs (e.g examination of subgroup of patients, post hoc nature of the analyses, different efficacy endpoints assessed in each trial). Of note these analyses were also lacking of a comparison against memantine monotherapy.

The DOMINO study did not show significant benefit in adding memantine to donepezil compared with memantine monotherapy in AD treated patients. After 52 weeks of follow-up there was no significant benefit of adding memantine to donepezil with respect to scores on cognition (MMSE 0.8 points higher with memantine than with placebo; 95% CI, −0.1 to 1.6; p=0.07) or on the activities of daily living (BADLS 0.5 points lower with memantine than with placebo; 95% CI, −2.2 to 1.2; p= 0.57). These data reinforced the uncertainties over the efficacy of the combination and its place in the AD therapy. It also further questioned the use of the proposed fixed combination (memantine 20 mg/donepezil 10 mg) as a substitution indication in the absence of robust data demonstrating the efficacy of the combination in the intended population.

Treatment guideline/expert panel recommendations on management of AD vary across European Union. Notably, 2 recent European publications ie “NICE technology appraisal guidance 217: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer’s disease” and “EFNS Guidelines for the diagnosis and management of Alzheimer’s disease, 2010” stated that the benefits of adding memantine to AChE inhibitors were not clear with the currently available data. Moreover, the conclusions of the NICE review were that *“combination treatment with memantine and AChE inhibitors could not be recommended because of lack of evidence of additional clinical efficacy compared with memantine monotherapy.*

Whilst the presented bibliographical analysis had some methodological limitations (e.g. retrospective access to the data, lack of randomization, limited number of countries or patient population involved), they indicate that memantine and AChEIs (mostly donepezil) are being prescribed as a combination therapy for AD. However their clinical use varies considerably across the EU. The differences could be explained by the limited efficacy of available treatments for the treatment of AD, the lack of consensus in the therapeutic recommendations in force in each country, the differences in the financial supplies of medicines or in the local organization of health systems. These findings also indirectly correlated with the heterogeneity seen among available treatment guidelines/expert panel recommendation.

Risks

Unfavourable effects

The most frequently reported AEs in the subjects receiving the combination included agitation, fall, confusional state, dizziness, diarrhoea, headache, upper respiratory tract infection and urinary tract infection. Many of the most common AEs were known to be commonly associated with AD (confusion, agitation, depression). Other AEs less likely to be disease related were nausea, vomiting and diarrhoea. The majority of AEs was of mild to moderate intensity and did not lead to discontinuation of study medication.

The overall incidences of AEs were similar in the MEM/DPZ and PBO/DPZ groups in the short-term exposure, except for confusional state and headache that were more frequent in the combination group. The incidence of most of AEs reported with MEM/DPZ increased with the exposure. Unlike

donepezil monotherapy group (in which AEs rates decreased over time), patients treated with the combined therapy showed significantly higher incidence of nervous, digestive and urinary tract disturbances in long term treatment.

Postmarketing data suggested an increased risk of fall, convulsion and tremor for the combination as compared to memantine. On the basis of a qualitative comparison, the overall AE profile appeared to be comparable between the combination and memantine group. However, among moderate to severe AD patients, the incidence of confusion and fall in patients with the combination was higher than in patients with memantine monotherapy.

Uncertainty in the knowledge about the unfavourable effects

There were limited uncertainties. The safety profile of the combination (memantine/donepezil) is adequately characterised, considering the AE profiles of the individual components.

Considering the well characterised AE profiles of the individual components, no new relevant safety findings were noted when memantine and donepezil were concomitantly used.

Benefit-risk balance

Importance of favourable and unfavourable effects

Whilst the simplification of therapy and as a consequence the improvement of the compliance and adherence to therapy are well-recognized benefits of the fixed combinations, this treatment option for AD remains questionable in view of the uncertainties over the efficacy of the combination and its place in AD therapy.

These uncertainties did not support the use of the fixed combination as a substitution indication in the treatment of adult patients with moderate to moderately severe AD (MMSE 10-19). Although it is acknowledged that the targeted population covered a group of patients for which memantine and donepezil are currently authorised and the simplification therapy is the intended use, to what extent each active component independently contributes to the efficacy and safety of the combination in the intended population is currently unknown.

The data on simultaneous use of memantine 20 mg and donepezil 10 mg across the European Union are insufficient to support a substitution indication for the fixed combination in the treatment of moderate to moderately severe Alzheimer's disease.

Benefit-risk balance

Having considered the favourable and unfavourable effects of the fixed combination (memantine 20 mg/donepezil 10 mg), the CHMP concluded that the benefit risk balance for Acrescent was negative for the following reasons:

- The efficacy of the combination (memantine 20 mg/donepezil 10 mg) versus the components administered individually in the treatment of moderate to moderately severe Alzheimer's disease has not been sufficiently demonstrated
- The data on simultaneous use of memantine 20 mg and donepezil 10 mg across the European Union are insufficient to support a substitution indication for the fixed combination in the treatment of moderate to moderately severe Alzheimer's disease.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Acrescent in the treatment of moderate to moderately severe Alzheimer's disease who are already on stable daily dose of 20 mg memantine and 10 mg donepezil , the CHMP considers by consensus/majority decision that:

Whereas

- The efficacy of the combination (memantine 20 mg/donepezil 10 mg) versus the components administered individually in the treatment of moderate to moderately severe Alzheimer's disease has not been sufficiently demonstrated
- The data on simultaneous use of memantine 20 mg and donepezil 10 mg across the European Union are insufficient to support a substitution indication for the fixed combination in the treatment of moderate to moderately severe Alzheimer's disease.

the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Acrescent.