SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Axura. For information on changes after this date please refer to module 8.

1. Introduction

Merz Pharmaceuticals GmbH have submitted a Marketing Authorisation Application for the medicinal product memantine, tablets and oral solution for the treatment of patients with moderately severe to severe Alzheimer's disease and vascular dementia.

Dementia is a chronic progressive organic mental disorder in which there is a disturbance of multiple higher cortical functions. From epidemiological studies, it is estimated that there are approximately three million individuals with dementia in the European Union. Dementia is characterised by dysmnesia, intellectual deterioration, changes in personality and behavioural abnormalities. It is not only a problem for the patient but also responsible for making the patient dependent on his family or the community.

There are two main forms of dementia, Alzheimer's Disease (AD) and dementia with vascular origin (VaD). Dementia of the Alzheimer type is the most common cause and accounts for 50-60% of severe dementia cases and Vascular Dementia (VaD) for about 10 to 20%, 20% of patients have both disorders. 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. The cause of the disease remains unknown although some biological and anatomical factors have been identified and are the basis for current and proposed therapies.

Current drug therapies for Alzheimer's disease include acetylcholinesterase inhibitors such as tacrine, donepezil, rivastigmine and galanthamine. All of these increase cholinergic synaptic transmission by inhibiting acetylcholinesterase at the synaptic cleft. Tacrine was the first of the acetylcholinesterase (AchE) inhibitors to be approved. Donepezil was authorised later in 14 EU Member States. Both medicinal products have the same indication: Symptomatic treatment of mild to moderate dementia of the Alzheimer type. Rivastigmine has been authorised through the centralised procedure and galantamine through the Mutual recognition procedure in 14 Member States. They both have been approved for the following indication: Symptomatic treatment of mild to moderately severe dementia of the Alzheimer type.

The Note for Guidance on Medicinal-Products in the Treatment of Alzheimer's disease (CPMP/EWP/553/95) is mainly applicable to mild to moderate Alzheimer's disease but may be adapted for use in preparing guidance for drug trials in other specific forms of dementia.

Memantine is a non-competitive NMDA glutamate receptor antagonist. The excessive release of glutamate is claimed to be associated with neurodegeneration in acute and chronic disorders such as hypoxia, ischaemia, stroke and perhaps Alzheimer's disease.

Memantine has been on the market in Germany for about 20 years. As a consequence some of the available data come from old studies performed during the initial development. Substantial new data have been produced specifically for this centralised procedure.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

There are two pharmaceutical forms, film-coated tablets 10 mg and oral drops solution 1%w/w:

Film-Coated Tablets
The tablets are white to off-white coloured, biconvex, oblong tablets. The excipients chosen for the core tablet formulation were lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, talc and magnesium stearate, and for the film-coating formulation were methacrylic acid – ethyl acrylate copolymer (1:1), sodium lauryl sulphate, polysorbate 80, triacetin, simethicone emulsion and talc.
Tablets are packaged in clear polypropylene (PP) / aluminium foil blisters (350µm/15µm). The blister contains 10 or 20 tablets and the package sizes are 30, 50 or 100 tablets.

Oral Drops Solution
The drops consist of an aqueous solution of the active substance in a sweetened base, preserved against microbial spoilage with potassium sorbate. The drops are presented as a clear, colourless solution in amber glass bottles containing 20, 50 and 100 ml of solution. The bottle contain a polyethylene dropper and polyethylene screw cap.

Active substance

Memantine hydrochloride is 3,5-dimethyl-1-adamantamine hydrochloride. It is an 'established' or known active substance, although it is not described in the PhEur. It is a white crystalline odourless powder, soluble in water. structure has been confirmed by the synthetic route, elemental analysis, IR absorption spectrum, ^{1}H-NMR and ^{13}C-NMR spectra. The molecule has 2 chiral centres but since there is a plane of symmetry between them the molecule is not chiral. Samples of memantine hydrochloride have been crystallised in relevant solvents and tested by X-ray powder diffraction. According to these studies, no polymorphism is shown.

Information about the manufacturing process has been presented by the manufacturer in an EDMF. It is synthesised via 3 steps. Major impurities are, intermediate products and those degradation products which occur during production and purification.

Active Substance Specification

The following tests are carried out: characteristics, identification, assay as well as several tests for purity such as solubility, loss-on-drying, heavy metals, related impurities, residual solvents, particle size etc. Validation studies are based on the relevant ICH guideline and batch analytical data on 12 batches confirm conformity to the specifications.

Stability

Stability data on five batches of drug substance have been provided. The stability studies have been performed under 'accelerated' conditions at 40ºC /80% RH for 26 weeks and 'room temperature' (20-25ºC) conditions for up to 208 weeks. The active substance is an old established substance and stability studies were initiated before the finalisation of the CPMP/ICH guidelines. While storage conditions and sampling time are not according to the ICH stability guideline, the accelerated conditions are slightly harsher than those foreseen by ICH and are considered to be acceptable.

Testing under stress conditions indicates that the substance is highly stable and only degrades under severe oxidative conditions and elevated temperature. From the studies it is concluded that Memantine HCl does not require special storage conditions. The proposed packaging material for the bulk substance is justified at room temperature.

Finished products

1. Film-coated tablets

Other ingredients
The excipients chosen for the core tablet formulation were lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, talc and magnesium stearate, and for the film-coatin formulation were methacrylic acid – ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate, triacetin, simethicone emulsion and talc.

All the excipients are controlled by monographs in the PhEur, except simethicone emulsion that is controlled by a USP monograph. The magnesium stearate is from plant origin and therefore there is no significant risk of TSE/BSE transmission.

Product development and finished product
Memantine tablets had been on the German market for more than 15 years at the time of application. During this period, the pharmaceutical development was focused on various modifications of the initial formulation in order to improve its quality:

- Introduction of a first organic then aqueous film-coat to mask the unpleasant taste;
- Change of tablet shape from round to oblong with a break-line to get an easily divisible tablet that facilitates the dosage (5 and 10 mg).

A standard method of manufacture is employed for the manufacture of the tablet cores, compression into tablets and film-coating. The process involves two stages: production of uncoated tablets and film-coating of uncoated tablet cores. This process was validated on 5 industrial batches.

The finished product is tested for appearance, identification, assay, dissolution, impurities and microbiological purity etc.. Batch analysis data for three production scale batches show compliance with the set specifications.

Stability of the Product
Stability tests have been carried out on six batches of finished product. All batches were packaged in the packaging proposed for marketing. Conditions studied were 25ºC/ 60%RH, 30ºC/ 60%RH, 40ºC / 75% RH for up to 12 months.Parameters tested include the usual tests for assay, degradation products and dissolution etc. No evidence of significant degradation or physical instability was found. In total, the stability results support the shelf-life and storage conditions as defined in the SPC.

2. Oral drops solution

Other ingredients
Sorbitol is present as a flavouring agent, and also potassium sorbate as preservative, dissolved in Purified Water. All these ingredients comply with PhEur requirements.

Product development and finished product
The formulation is standard, and the manufacturing process is simple. A bioequivalence study has been performed to demonstrate that the tablets and oral solution are bioequivalent at equivalent doses (10 mg orally). The parameters measured in each case showed no differences which could be regarded as statistically significant or clinically relevant. A summary is given in the clinical section of this report.

The release specification includes tests for identity, assay of active substance, preservative content, etc., and sufficient batch data exist to demonstrate uniformity of product from batch to batch.

Stability of the Product
The stability of the product has been shown on three batches stored at 25ºC/ 60%RH, 30ºC/ 70 %RH, and 40ºC / 75% RH for up to 5 years. Parameters tested include the usual tests for assay, assay of preservative, degradation products etc. All results enclosed are within specifications in all batches studied. In total, the results support the shelf-life and storage conditions as defined in the SPC.

In-use stability of the finished product:
The proposed shelf-life after opening is justified on the basis of physicochemical and microbiological grounds, and this is also mentioned in the SPC and on the label.

Discussion on chemical, pharmaceutical and biological aspects

In summary, the manufacture and control of the active substance and finished products have been validated, and indicate satisfactory product uniformity at release. Quality characteristics relevant to clinical use have also been investigated during the shelf-life studies, and are satisfactory for products of this type.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Glutamate is the principal fast neurotransmitter in the brain, where up to 40% of all synapses are glutamatergic. Like most neurotransmitters, it is released by action-potential-induced exocytosis into the synaptic cleft, from where it activates the post- synaptic receptor. Two types of receptors, ionotropic and metabotropic, bind and respond to glutamate. There are three major subtypes of ionotropic receptors: AMPA, Kainate and N-methyl-D-aspartate (NMDA) receptors. The NMDA receptor is a voltage-sensitive, glutamate-gated ion channel, which permits passage of Ca^{2+} into the neuron after the neuron has been depolarised by AMPA/kainate receptors.

Memantine is a non-competitive NMDA receptor antagonist, which acts selectively at NMDA receptors in brain and retina, but has no activity at AMPA/Kainate receptors. Published literature indicates that neurodegenerative diseases such as dementia of the Alzheimer type (AD) have a common pathogenic mechanism, namely impaired glutamate homeostasis.

Several studies have been carried out *in vitro* and *ex vivo* and *in vivo* in rat, mouse, gerbil, guinea pig, cat and dog to study the preclinical pharmacology of memantine. The pharmacodynamic models and the biostatistical analysis comply with internationally accepted procedures in pharmacology and most of the relevant studies have been published in peer-reviewed journals and monographs.

- *In vitro studies*

Several studies have been conducted to assess the binding of memantine to the NMDA receptor. In human embryonic kidney cells transiently transfected with NMDA receptor subunit combinations, memantine concentration-dependently blocked L-glutamate-mediated currents. Relatively high concentrations of memantine were required to show neuroprotective activity in an *in vitro* model of acute ischaemia, although memantine was shown to be superior to dizocilpine.

- *In vivo studies*

Memantine reduces neuronal damage induced in various global and focal ischaemia models in laboratory animals. However, in most cases memantine was administered before the occlusion, and the effective doses were higher (10-20 mg/kg) than considered therapeutically relevant in man.

In rats, bilateral carotid artery occlusion for 60 minutes resulted in learning deficits in the Morris maze. Prior treatment with memantine 30 mg/kg i.p., 10 min before surgery completely prevented this functional deficit. Similarly, memantine 20 mg/kg reduced the four vessel occlusion ischaemia-induced deficits in the Morris maze and reduced neuronal damage in the hippocampus. Memantine was shown to be neuroprotective against acute damage induced by the endogenous NMDA receptor agonist quinolinic acid injected to the hippocampus.

Several studies were also conducted on the neurotoxic effects of glutamate in structures known to be affected in learning. Memantine administered i.p. before NMDA microinjection produced a clearcut protection from the neurotoxic effects of direct injections of NMDA. Inflammation might also play a significant role in the pathogenesis of AD and vascular dementia. Continuous infusion of memantine by minipump at therapeutically relevant dose prevented clearly neuronal loss induced by inflammation leaving inflammatory reaction unaffected.

In moderately aged rats, memantine prolonged the duration of long-term potentiation (LTP) *in vivo* and also showed a trend to improve memory retention in the Morris maze. Similar positive effect of memantine were seen in rats showing learning deficits as a result of lesions in entorhinal cortex, which is a brain region affected at early stages of AD. NMDA-induced amnesia was also antagonised by memantine.

As secondary pharmacological effects, memantine showed *in vitro* anticonvulsive properties in guinea pig brain slices qualitatively similar to those of dizocilpine, but 10-100 fold less potent. At high doses *in vivo* in kindled rats, it is proconvulsive. Memantine is analgesic in rats under certain circumstances, consistent with the presence of NMDA receptors on superficial spinal dorsal horn neurons, normally modulated by tonically active glutamatergic supraspinal descending systems.

- *Pharmacodynamic drug interactions*

Drug-induced alterations in bile flow and urinary pH may affect memantine kinetics which is adequately addressed in the SPC. No significant drug-drug interaction between memantine and a range of selected substrates routinely used to phenotype drug-metabolizing enzyme activities in man were observed.
Although the preclinical interaction studies with memantine are limited, interactions studies have been conducted in humans during the clinical trial program including most of the relevant drugs used for this therapeutic indication such as amantadine, cimetidine, triamterene, hydrochlorotiazide, ketamine, L-dopa, anticholinergics and dopaminergics, barbiturates, neuroleptics, antispastics and acetylcholine esterase inhibitors (AchEI).

- *General and safety pharmacology programme*

Safety pharmacology studies were performed on mice, rats guinea-pigs and dogs. The major clinical sign was ataxia, preceded by increased locomotor activity. Memantine inhibited ocular-electroshock-induced seizures but potentiated pentetrazol-induced (GABA-mediated) seizures. There were limited mixed effects on intestinal contractility, and no notable effects on the cardiovascular system. Increased hexobarbital-sleep time is presumed to indicate inhibition of cytochrome P450 enzyme CYP2B1. The results of these screening tests show that memantine has relatively minor peripheral pharmacological effects; the primary target organ appears to be central nervous system.

Pharmacokinetics

Different non-clinical ADME studies have been conducted in mice, rats, rabbits, dogs, mini-pigs, and monkeys to characterise the pharmacokinetic profile of memantine in the animal species chosen. The routes of administration selected were oral and intraperitoneal.

Memantine is completely absorbed from the gastrointestinal tract and the plasma concentrations are proportional to dose. The mean plasma protein binding of memantine is 41% in the rat compared to 45% in humans.

Distribution studies with memantine have been carried out in rats and baboons. After single and repeated administration, memantine is distributed through all tissues, with increased affinity to the kidneys and lungs. A 12-month chronic treatment of rats with memantine in the diet resulted in highest levels in lung, spleen, kidney and lachrymal gland, slightly lower in the brain and spinal cord, liver, lymph nodes, pancreas and salivary glands.

Following infusion of memantine whole brain concentrations were 44-fold higher than free concentrations in the serum. The free brain ECF concentration of memantine (0.83 ± 0.05 μM) corrected for *in vivo* recovery (39 %) was comparable to free serum and CSF concentrations.

The plasma pharmacokinetics of memantine after oral administration in the rat shows two peak concentrations, 0.5-1 and again 2-4 hours after dosing, which could be explained by biliary uptake and enterohepatic circulation. In mice, however, biliary excretion of memantine is minimal (<4%).

There is no significant change in the distribution of memantine after long-term administration, and no major increase or decrease in plasma or organ concentrations.

Memantine metabolites are mainly hydroxylated, with an intact or oxidised amino function. In addition, conjugated compounds were found as phase II metabolites but they seem to be of minor importance. MRZ 2/373 (1-amino-3-hydroxymethyl-5-methyl-adamantane) appears to be the major urinary metabolite detected in the rat whereas in the baboon ring hydroxylated metabolites (MRZ 2/371, 2/374) are predominant. The metabolites MRZ 2/371, 2/373, 2/374 and 2/375 identified in human urine had no NMDA antagonistic activity, or this activity was much lower than that of memantine; pharmacological activity is therefore attributable to memantine alone.

Memantine and its metabolites are excreted primarily via the kidney. After a single oral dose of ^{14}C-memantine, minimum 80-90% of the excreted radioactivity was excreted in the urine in animals and humans. Memantine is partly excreted by tubular secretion. Impaired kidney function may thus have a similar impact on memantine elimination in man. It is stated in the SPC that memantine must be adjusted on an individual basis, including monitoring of kidney function in patients with renal insufficiency. It is not recommended in patients with severe renal impairment. Elimination half-life was approximately 4 hours in all species except man where terminal elimination half-life was approximately 100 hours.

Toxicology

A complete non-GLP preclinical toxicology program was conducted on memantine in the 1970s, consisting of single-dose and, repeated-dose studies in rodents and dogs and baboons by s.c., i.p., i.v. and oral administration of memantine. All of the preclinical toxicity studies, which are required to fulfil current requirements, were repeated as GLP studies in the 1980s and 1990s and there is good agreement between the older non-GLP and the more recent GLP study data.

Single dose toxicity
The acute toxicity of memantine was evaluated in rats and mice. Toxic symptoms were similar by all administration routes: ataxia, tremor, prone position and bradypnea. No persistent clinical signs were seen in survivors 14 days after acute high dose memantine treatment. In an acute oral toxicity study in dogs, only central nervous system symptoms such as ataxia, tremor, prone position and convulsions were seen. Mild ataxia was reported at 5 mg/kg, tremors and minor seizures at 25 mg/kg. At 50 mg/kg, one male died on the second day after treatment; both male and female had coarse tremor and intermittent clonic seizures. At 75 mg/kg, both died within 6 hours, after coarse tremor and strong clonic seizures. Surviving animals recovered within 3 days, and no persistent changes were seen 14 days after treatment.

Repeated dose toxicity
The four major preclinical concerns referred to toxic effects found in different animal species. The most prominent clinical sign in all species tested was ataxia, followed by reduced body weight, with food consumption unchanged or increased. At high doses in rat and dog, prolonged prothrombin times, decreased thymus, spleen weights, reduced blood platelets and, reduced blood protein and lymphocytopenia were seen. No significant effects on haematology or clinical chemistry were observed in the studies on monkeys. An increased prevalence of pulmonary foamy macrophages was noted at high doses of memantine in rodents. In the 12-month rat study, electron microscopic examination of the eye tissues showed findings of abnormal lysosomal storage (granules) in ganglion cells and in pigment epithelium cells only. Neuronal vacuoles (not related to Olney lesions) in the central nervous system were seen, at lethal dose levels in the 13-week dietary mouse study. Most toxicological findings are suggested to be species-specific and/or to appear at doses well in excess of the therapeutic dose.

Genotoxicity
Genotoxicity was tested in a four standard assays system: gene mutation assays in bacterial and in mammalian cells; chromosomal mutation assays in mammalian cells in vitro and in-vivo. Memantine was not mutagenic or clastogenic in any test system. For chemical reasons NO-metabolites are not likely to form nitrosamines and therefore, from this perspective, there should be no concern for genotoxicity or carcinogenicity and, preliminary data indicate that these putative metabolites are detectable only in trace amounts in human urine derived from-treated volunteers.

Carcinogenicity
Two carcinogenicity studies have been conducted in rats and mice: In a 30-month dietary carcinogenicity study in rats, survival was not adversely affected by treatment. Decreased body weight, dyspnea, foamy macrophages in the lung, and mineralization of renal medulla were observed. Type and incidence of neoplastic lesions did not differ between treatment and control groups.

In a 24-month dietary carcinogenicity study in mice survival was not adversely affected by treatment. Reduced body weight, increased food consumption and dyspnea were evident. There were no treatment-related histopathological findings. Type and incidence of neoplastic lesions did not differ between treatment and control groups. Memantine can thus be considered as non-carcinogenic.

Reproduction toxicity
Reproductive performance of rats was examined after treatment in all segments of the reproductive cycle in a series of three studies all using the same doses: 2, 6 and 18 mg/kg/day. At 18 mg/kg and occasionally also at 6 mg/kg, reduced food consumption and body weight gain were observed in all studies. Except for marginal foetal growth retardation at 18 mg/kg, no effects were seen on any aspect of reproduction. Embryo-/foetotoxicity of memantine was tested in the rabbit after oral administration. No specific adverse effect on reproduction was observed for memantine.

Local tolerance
Local tolerance to memantine after intravenous, intraarterial, intramuscular or paravenous injection was tested in dogs. Paravenous injection caused slight oedema, which was still visible after 48 hours. No other reactions were seen. Local tolerance is considered good. The sensitising potential was tested in guinea pig, after epicutaneous administration of memantine. Memantine displayed neither irritation nor sensitisation potential.

Ecotoxicity/Environmental risk assessment
Memantine is administered to humans at doses of usually 20 mg/day. 70% of the ingested drug are excreted unmetabolized in the urine. The metabolites are water-soluble and not biologically active or toxic. From their chemical structures no persistence in the environment can be assumed for the parent compound or its derivatives. Therapeutic used of memantine is estimated to lead to concentrations below one part per billion at the point of entry into the aquatic environment. An environmental risk can be excluded.

4. Part IV: Clinical aspects

Clinical pharmacology

There are a total of 25-pharmacodynamic/pharmacokinetic studies with memantine. These studies have included 434 subjects, 377 of them received memantine and 105 received placebo (some volunteers/patients received both in cross-over studies). Of these clinical pharmacology studies, 2 were performed in patients with neurological disease/dementia syndrome, 2 in healthy elderly subjects, one in elderly subjects with renal impairment and 20 in healthy volunteers. A total of 11 single dose studies have been performed, with memantine administered orally or intravenously at doses up to 60 mg. The remaining 14 studies were multiple-dose studies, with doses of memantine up to 60 mg orally.

Pharmacodynamics

No specific pharmacodynamic endpoint to correlate with the therapeutic effect in healthy volunteers has been identified. A single dose of 30 mg does not impair physiological NMDA neurotransmission (information processing and memory functions) in healthy volunteers (MRZ-9405). Daily doses of 20 mg memantine showed no effect on perception of experimental pain stimuli or primary and secondary hyperalgesia (MRZ-9502). No consistent effects of memantine on EEG were obtained in a study with memantine 30 mg iv (MRZ-8610).

In another study in elderly subjects, a decrease of vigilance under placebo and stabilisation under memantine was observed (MRZ- 8909). Study MRZ-9402 with 49 elderly subjects showed no effect on pituitary function (TSH, LH, FSH, prolactin and vasopressin) with a dose of 20 mg of memantine during 27 days.

Two studies were performed exploring the dose-effect of memantine on cardiovascular function in a total of 9 healthy volunteers. With single doses of memantine up to 60 mg i.v. (MRZ-Z040) small, non dose-dependent decreases in cardiac performance index and systolic blood pressure were observed. In another small study (MRZ-Z041) an increase in blood pressure had also been observed. In addition to the results of these pharmacology studies (MRZ-Z040/Z041), the large phase III trials provided data on blood pressure that do not show any significant difference between placebo and memantine on blood pressure. No effects on cardiac conduction were found with memantine in clinical pharmacology studies. The phase III study MRZ-9408 performed an analysis of ECG, which showed no prolongation of QT interval after 6 months treatment with memantine.

As memantine is secreted in small amounts via lacrimal gland, a study (phase II open study MRZ-9100) was performed to examine if memantine had any effects on the eye in patients with detectable levels of memantine in lacrimal fluid. A total of 10 elderly patients with brain dysfunction were included taking 20 mg/day during a mean of 47.9 months. It was concluded that no evidence of eye alterations was found. These results were confirmed by opthalmological examination after 6 months of treatment with memantine 20 mg in a phase III study (MRZ-9202). However, as the preclinical ocular findings raised some concerns, the applicant will provide on an annual basis the CPMP with safety analysis of two large placebo-controlled studies in glaucoma patients.

Some data on safety were collected from these clinical pharmacology studies. The reported adverse events were tiredness, headache, dizziness, somnolence, impaired concentration, dry mouth, agitation and nausea.

Pharmacokinetics

Absorption
Memantine is well absorbed, with high bioavailability approaching 100%. Time to maximum plasma concentration (t max) following single oral doses of 10 to 40 mg ranges between 3 to 8 hours respectively. Peak plasma concentration (Cmax) following a single 20 mg oral dose of memantine ranges between 22 and 46 ng/ml. AUC and Cmax appeared to increase in a dose proportional manner. Steady state levels are reached around day 11 with accumulation in plasma resulting in approximately 3-4 times Cmax compared with that following a single dose. In phase III trials, memantine 20 mg daily results in steady-state plasma concentrations ranging from 70 to 150 ng/ml with marked inter-individual variation.

Distribution
The volume of distribution of memantine is approximately 9 l/kg suggesting extensive distribution of memantine into tissues. Memantine is bound to plasma-proteins at approximately 45% (HUK 610-13). Memantine rapidly crosses the blood-brain barrier: Following a 20 mg infusion to 9 male subjects, memantine was detected in cerebrospinal fluid (CSF) within 30 minutes (MRZ-8609). Daily doses of 5-30 mg memantine to patients resulted in a mean CSF/serum ratio of 0.52. A post-mortem analysis of distribution of therapeutic doses of memantine (20 mg/day) in one female patient did not demonstrate any localised tissue-distribution. Concentrations in different regions of the brain varied between 0.1 and 0.5 µg/g.

Metabolism
The majority of the administered memantine dose is excreted unchanged in urine (75-90 %), with the remaining memantine converted to numerous metabolites. The major metabolites of memantine excreted in urine are the memantine N-gludantan conjugate, 4-and 6-hydroxy memantine and 1-nitroso-deaminated memantine. Both *cis*- and *trans*- isomers of hydroxy memantine were observed in the urine. The memantine metabolites are hydroxylated and N-oxidized derivatives of memantine. The human metabolites tested thus far in cell patch clamp studies, did not have NMDA antagonistic activity, or this activity was much lower than that of memantine, as their IC_{50} values were greater than 90 times the IC_{50} value of memantine.

Elimination
Memantine is mainly excreted unchanged in the urine (60-80%) and its terminal half-life is 60 to 100h. In volunteers with normal kidney function, total renal clearance amounts to 170-ml/min/1.73 m^2 In a study in elderly volunteers with impaired renal function (creatinine clearance approximately 50 ml/kg/1.73 m^2), a significant correlation was observed between creatinine clearance and total renal clearance of memantine. Total renal clearance substantially exceeded renal clearance by filtration, thus indicating that a significant part of renal clearance is due to secretion instead of filtration. Memantine and its metabolites are mainly excreted via the kidneys (75-90%) and around 10-25% of the dose was recovered in the bile and faeces. Renal excretion is higher at acidic urine pH (4.96-5.27) compared to alkaline (7.62-8.18) conditions (7-9 fold higher) indicating that the urine pH is a major factor influencing renal clearance of memantine. Changes in urinary flow have a statistically significant influence on renal excretion of memantine, but the clinical relevance seems to have a minor importance (MRZ-9601). When steady state conditions have been established, alterations of the urine pH towards alkaline conditions may lead to an accumulation of the drug with a possible increase of side effects. Considerable changes in dietary habits that lead to changes in urinary pH may influence the renal excretion of memantine (MRZ-9601). Some diet restrictions are therefore necessary. For instance, a drastic change to vegetarian diet should be avoided during treatment with memantine because the urine pH changes to alkaline could lead to an accumulation of the drug. A minority of memantine is eliminated via sebaceous, lachrymal, and salivary and sweats glands (MRZ-9203).

- Interaction studies:

Metabolism and hepatic clearance contribute to a minor degree to the elimination of memantine. *In vitro* testing of drug-drug interactions in human liver microsomes did not show any interactions between memantine and numerous enzymes commonly involved in drug metabolism (CYP 2A6, CYP 2C9, CYP 2D6, CYP 2E1, CYP 3A, CYP 1A2, flavin containing monooxygenase, epoxide hydroylase and sulfphation *in vitro*)–indicating a low potential for metabolic drug-drug interactions with memantine.

Tubular secretion of memantine occurs via the same transport pathways as for amantadine, cimetidine and probably triamterene. Other drugs such as ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels. In a cross-over study of 20 healthy volunteers, the tested drugs hydrochlorothiazide (HCT) and triamterene had no influence on the pharmacokinetics of memantine. Vice versa, memantine had no relevant influence on the pharmacokinetics of triamterene. However, for HCT a pharmacokinetic interaction with memantine could be demonstrated (MRZ-9702) and there may be a possibility of reduced diuretic effect of HCT.

According to one published report, concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA antagonists. Though there are no published reports, the same may be true for ketamine (used as an anaesthetic agent) and dextrometorphan. There is one publication on a possible risk also for the combination of memantine and phenytoin.

The mode of action suggests that the effects of anticholinergic agents, L-dopa, and dopaminergic agents may be enhanced by memantine. The effects of barbiturates and neuroleptics may be attenuated.

Concomitant administration of the antispastic agents dantrolen or baclofen can modify their effects, thus a dosage adjustment may be necessary. In a recent in vitro study, memantine did not interact with acetylcholine esterase inhibitors (donepezil, tacrine, galantamine) in therapeutically relevant concentrations. These recommendations are thus mainly based on theoretical considerations.

In clinical trials, no interactions with the following concomitant medication could be found: acetylsalicylic acid, tocopherol, donepezil, paracetamol and chloral hydrate. In keeping with the low potential for drug-drug interactions with memantine, in the overall safety database (ISS) there was no evidence of any specific drug-drug interactions, with no medically relevant differences in the frequency of adverse events experienced with or without a wide variety of concomitant medications used in the elderly population. The absorption of memantine is unaffected by food.

Pharmacokinetics in Special populations
Elderly: Studies conducted in young healthy subjects and in elderly healthy subjects, suggest that the pharmacokinetics of memantine are only slightly different with age and that these differences are mainly due to variations in body weight and fat.

Patients with renal impairment: In agreement with the predominantly renal elimination of memantine, clearance of memantine showed a dependence on renal function. When a single 20 mg oral dose of memantine was administered to geriatric subjects with different levels of renal function (40 to >80 mL/min/1.73 m^2), a significant correlation was observed between creatinine clearance (renal function) and total clearance of memantine. In subjects with normal kidney function, total clearance averaged 161 mL/min and there was a significant decrease with increased degree of renal impairment ($p < 0.01$). Total renal clearance of memantine substantially exceeded renal clearance by filtration, indicating that renal clearance is due in part to secretion. The amount of memantine excreted in urine from 0 to 48 hours post-dose was significantly reduced with renal impairment ($p < 0.01$). No significant relationships were observed for $T_{1/2}$ and C_{max} values versus creatinine clearance.

Based on these results a reduction of the dose to 10 mg/day is recommended in the SPC for patients with moderately reduced renal function.

Patients with hepatic impairment: The effect of liver disease on the pharmacokinetics of memantine has not been studied. As memantine is metabolised to a minor extent only, and into metabolites with no NMDA-antagonistic activity, clinically relevant changes in the pharmacokinetics are not expected in mild to moderate liver impairment.

Children: Pharmacokinetics of memantine have not been studied in subjects less than 18 years of age.

- Bioequivalence studies:

Study MRZ-9201 was a three-way cross-over study in 12 healthy adult male volunteers. Subjects received 20 mg memantine in the form of 2 tablets or 40 drops or 1 controlled release tablet as single oral doses at intervals of 2 weeks. The pharmacokinetic parameters for memantine tablet and solution (mean ± standard deviation, n=12) are given in the following table:

	$AUC_{(0-\infty)}$ [ng•h/mL]	CI 90%	C_{max} [ng/mL]	CI 90%	t_{max} [h]	$t_{½term}$ [h]
Tablet 20 mg	1870 ± 352	0.99-1.21	26.00 ± 4.07	0.93-1.07	3.25 ± 1.74	68.9 ± 21.6
Solution, 40 drops	2030 ± 312		26.00 ± 4.22		3.33 ± 1.93	74.3 ± 23.8

Comparison of the bioavailability of memantine from a 10 mg immediate release tablet and from an oral solution (drops) showed that these two formulations were bioequivalent based on the 90% confidence intervals for the AUC and C_{max} parameters.

Clinical efficacy

A total of 25 clinical studies with memantine in 4428 patients with dementia or dementia syndrome are mentioned in the dossier. 21 pilot studies involved small numbers of patients, different populations to those intended for memantine use or dose ranging. As these studies are not considered to contribute efficacy data in support of this application, these studies are not described in detail in the clinical efficacy part, but the safety data is included in the Global Analysis of Safety.

Four phase III studies provide data in relation to the efficacy and safety of memantine in moderately severe to severe AD and VaD. One of them (MRZ-9605) was performed following scientific advice provided by the CPMP. It was requested in order to confirm the results obtained in other studies (MRZ-9403). The advice recommended that a functional activity measure and a global outcome measure (such as CGI-C or CIBIC-plus) had to be considered as the two associated primary endpoints. These criteria could be usefully associated with behavioural assessment. In addition, as far as possible, the effect on cognition had to be assessed, as it should be made clear that the effects are related to the disease and are not unspecific effects.

Although all clinical trials were performed with memantine tablets, the solution could be considered bioequivalent (*see the bioequivalence section*) to the tablet formulation and therefore the results from the clinical trials are applicable for both the tablet and the solution formulations of memantine.

Pilot studies in dementia or dementia syndrome

The 21 pilot (proof-of-concept) studies of memantine in 3109 patients with dementia or dementia syndrome examined doses of memantine of 10-30 mg per day. Fourteen of the studies were double blind (11 placebo controlled, 3 ergotoxine substance controlled), 2 blind different-dose studies and 5 were open or drug monitoring studies. Memantine showed a statistically significant benefit in all pilot studies involving more than 65 patients. In summary, 7 of the 12 placebo controlled pilot studies showed statistically significant improvements in cognitive tests and behavioural evaluations, and 5 were negative. In the 3 short ergotoxine-substance-controlled studies, no statistically significant difference between the different treatments was demonstrated. Significant improvements in cognition and behaviour with memantine were observed in 3 of the 5 open or drug monitoring studies.Memantine was generally well tolerated with infrequent side effects, which were mild to moderate in severity and reversible. The adverse events (AEs) observed were similar to those reported by healthy volunteers and included dizziness/vertigo, restlessness, agitation/hyper excitation, fatigue, headache, and nausea.

Dose-response studies and main clinical studies

- **Dose response studies**

There is no formal placebo-controlled dose ranging study in the clinical development program of memantine. The choice of memantine 20 mg daily as a target for the phase III trials is supported by a dose finding analysis (MRZ-9501), which included one pharmacokinetic study (n=24) and 5 of the pilot studies in dementia syndrome (n=575). This analysis showed a dose response across the range of memantine 10 mg to 30 mg daily (and in a small number of patients on 60 mg), with more pronounced improvement in Sandoz Clinical Assessment Geriatric Scale (SCAG) with increasing dose, but with a dose-dependent increase in the number of AEs. This dose dependent increase in AEs was reduced when the daily dose was titrated up gradually. There are additional data from a long-term tolerability and safety trial (9406) in patients with impaired cerebral functional capacity. Study 9406 was performed in 147 patients, who were divided in three groups receiving different dosing regimens. It had a high number of dropouts by reasons apparently not related with the medication. These adverse events increased in frequency with 30 mg and 60 mg (11% and 18%) with respect to 15 mg (0%).

Theoretically, the choice of 20 mg is in line with a pharmacological rationale. According to published results the k_i –value (k_i = absorption constant) of memantine at its binding site on the NMDA-receptor is 0.5 µM in human frontal cortex.

Following short-term administration of memantine (up to 14 days) to elderly patients, the CSF/plasma ratio of memantine is around 0.5. Based on this and the observation of steady state plasma levels of memantine of 0.5-1.0 µM following 20 mg/day in phase I and III studies, 20 mg per day would be expected to result in CSF levels close to the k_i –value of memantine.

Trials in non-dementia indications
A list of trials in non-dementia indications is provided in the dossier. The safety data from these trials are included in the Global Analysis of Safety.

Main studies (phase III = therapeutic confirmatory trials)

The 4 phase III studies adhered to GCP Guidelines of the Committee for Proprietary Medicinal Products (CPMP) and Directive 91/507/EEC of the European Union. The studies were performed according to the Declaration of Helsinki, and in line with local ethical review board requirements for ethics and informed consent in this special population with advanced dementia. The study performed in Latvia (MRZ-9403) was audited by the competent German health authority.

Study Code	Doses	N	Population	Duration of treatment	Study design	Main objectives
MRZ-9605 (USA/1999)	20 mg	252	Moderately severe to severe AD	28 weeks	Multicentre, Randomised, Double blind, placebo contr.	1. CIBIC-plus (ITT-LOCF, p=0.064) 2. ADCS-ADL (ITT-LOCF, p=0.02)
MRZ-9403 (Latvia/1994)	10 mg	167	Moderately severe to severe AD and VaD	12 weeks	Multicentre, Randomised, double blind, placebo contr.	- CGI-C (p<0.001) - BGP (p=0.016)
MRZ-9202 (UK/1994)	20 mg	548	VaD	28 weeks	Randomised, double blind, placebo contr.	- ADAS-Cog (p<0.05) - CGI-C (n. s.)
MRZ-9408 (France/1996)	20 mg	288	VaD	28 weeks	Randomised, double blind, placebo contr.	- ADAS-Cog (p<0.05) - CIBIC -plus(n. s.)

MRZ 90001-9605
This study was designed according to CPMP scientific advice requested in 1998 in order to substantiate the results of study MRZ-9403 in AD patients.

Description of the study
Multicentre, double blind, randomised (1:1), placebo-controlled, parallel study design to enrol approximately 250 patients. All patients were to complete Visit 1(screen). At Visit 2(baseline, week 0), eligible patients were randomised to receive either placebo twice daily or memantine 10 mg b.i.d for 28 weeks. After completing the double-blind period of the study (28 weeks) all patients were given the opportunity to enter the 24-week open-label treatment period.

The inclusion criteria were outpatients aged more than or equal to 50 years with a diagnosis of probable AD (according to DSM-IV and NINCDS-ADRDA) with MMSE total scores between 3 and 14 points, GDS stages of 5 or 6 and at least FAST stage 6a. Dementia secondary to other conditions was to be excluded by physical, neurological, laboratory data, medical history and CT or MRI brain scan. Modified Hachinski Ischaemic Scale (HIS score more than or equal to 5) and CT or MRI brain scan together with medical history results were to be used for the exclusion of probable VaD. Major depressive disorder was to be excluded using the DSM-IV criteria. Patients receiving inadmissible medication (investigational drug, anticonvulsants, anti-Parkinson, hypnotics, neuroleptics/antipsychotics, acute administration of psychotropic drugs for enhancement of cognitive function include tacrine and donepezil) at screening could be included after an adequate wash-out period (usually 30 days; 60 days for investigational drugs)

Primary and secondary endpoints
The primary variables of efficacy were the global rating (CIBIC-plus) and a functional rating (modified ADCS-ADL css inventory). Secondary efficacy variables included the SIB (Severe Impairment Battery), MMSE, FAST (Functional Assessment Staging), GDS (Global Deterioration Scale), Modified ADCS-ADL srr Inventory, NPI (patient assessment and caregiver burden) and RUD (Resource Utilisation and caregiver burden).

Statistical analysis
Efficacy outcomes were analysed using the Wilcoxon-Mann-Whitney test for independent sample using the change from baseline in the patient's condition. Forthe confirmatory analysis, the outcome of interest was the change from baseline in the patient's condition. For each time point p-values and 95% confidence intervals for the difference between placebo and memantine group means and medians were to be presented.

Results

Study populations/accountability of patients
Two hundred and fifty two (252) outpatients with AD were randomised to double blind treatment and were included in ITT and safety subsets. 181 patients completed the double-blind period (84 of placebo patients and 97 of memantine), and 171 of these were included in the TPP subset (78 placebo patients and 93 memantine patients). The mean age of the patients was 76.33 years (SD 7.76, range 53-93) and 75.94 years (SD 8.40, range 50-92) in the placebo and memantine groups, respectively. The respective male/female ratios were 47/79 and 35/91 in the placebo and memantine groups. A total of 90% of the patients included were Caucasians, and between 95-95% of the patients in both groups had taken prior medications. Overall, 84% of placebo patients and 83% of memantine patients in the ITT subset had received prior treatment for AD. The two most common treatments received by both treatments groups were Aricept and vitamin E. Mean treatment duration for placebo was 193 days and for memantine 195 days. The safety subset included all patients who took study drug and the ITT subset included all patients randomised, whether or not they received treatment or the correct treatment. Seventy-one patients (71) discontinued the study. Adverse events (35 cases) were the most frequent reason for premature discontinuation.

Efficacy results
The two primary efficacy parameters were the CIBIC-plus global score and ADCS-ADL change in sum score. For the global endpoint (CIBIC-plus) a mean difference of 0.25 points was observed in favour of memantine. This difference is not statistically significant for the ITT population in the LOCF analysis (p=0.064) although it showed a strong trend. This result may be biased by the high number of discontinuations in the placebo group. At week 28, using the observed cases analysis for the ITT population ,there was a statistically significant difference (p=0.025) between the treatment groups in favour of memantine for CIBIC-plus.

Using the confirmatory LOCF analysis for the Modified ADCS-ADL Inventory css, a statistically significance difference (p=0.0217) in favour of memantine was found. These positive findings were confirmed for week 28 with observed cases and for the TPP subset analysis.

Two responder analyses were performed. Patients were classified as "responders" or "non-responders" based on their status in three domains (functional, global and cognitive) after 28 weeks of treatment. In the first analysis, a patient was classified as a responder if all three of the following criteria were met: 1) The CIBIC-plus score at week 28 was less than or equal to 4 (indicating improvement or no change). 2) The Modified ADCS-ADL css (change in sum score from baseline) at week 28 was greater than or equal to zero (indicating improvement or no change). 3) The change from baseline in the SIB score at week 28 was greater than or equal to zero (indicating improvement or no change). In the second responder analysis, a patient was to be classified as a responder if she or he met the CIBIC-plus criterion and either the Modified ADCS-ADL css criterion or the SIB criterion defined above. Analysis of both definitions of responders was performed in the ITT and TPP subsets.

For the first responder analysis (more stringent) there was no statistically significant difference between the treatment groups (p=0.1703), 11% of memantine and 6% of placebo were responders.
For the second definition there was a statistically significant difference (p<0.001) for the ITT subsets 29% vs 10%. A responder analysis performed *a posteriori* used the definition improvement or stabilisation in the cognitive domain (SIB) and in the global domain (CIBIC+). There was a statistically significant difference (p=0.0008) between the treatment groups with 21% of responders in the memantine and 6% in the placebo group. This definition of responder is similar to but not the same as that used during the CPMP assessment of Rivastigmine for the treatment of mild to moderate AD.

Secondary efficacy variables were SIB, MMSE, FAST, GDS, Modified ADCS-ADL sum scores of response, NPI and Resource Utilisation in Dementia. Only for the secondary efficacy measurements SIB and FAST, there was a statistically significant difference in favour of memantine for the ITT subset.

As recommended by the CPMP scientific advice, cognitive function was not a primary endpoint. However, the SIB scale was used as a secondary variableThe SIB change score from baseline to endpoint was statistically significantly different (p=0.0003) in favour of memantine. With memantine, mean scores fell –3.93 from a baseline value of 65.86(representing a 6% decline) compared with a fall of –9.84 from a baseline value of 68.33 with placebo (representing a 14% decline). A similar statistical improvement was not obtained in MMSE, a cognitive scale assumed to be less sensitive.

The study also involved a Resource Utilisation in Dementia (RUD) analysis. Mean monthly caregiver time was less with memantine (414 hours) compared with placebo (456 hours), (ANCOVA, TPP dataset: treatment difference –51.5, 95% CI –95.3 to -7.2, p=0.02). During the study, fewer memantine patients (1 patient) had to move from the community to an institutional setting compared with placebo (5 patients, log rank chi square, TPP dataset, p=0.05).

Open extension of MRZ-9605
Out of the 181 patients, who completed MRZ-9605, 175 patients (95 and 80 patients from the memantine and placebo arm, respectively) were treated with memantine (10 mg bid) for up to 6 months. Activities of daily living and global impression of change were assessed after 12 and 24 weeks of open, extended treatment. The treatment code during the previous double-blind period was revealed to patients and physicians only at the end of the full 12-month trial period (or at premature discontinuation).

The results of the extension phase of study MRZ-9605 show some apparent improvement in the deterioration rate (on both primary variables and SIB) of those patients on placebo that, after the end of the blinded phase, are switched to memantine so that their status approaches, over the weeks, the status of the patients continuing on memantine. Although open label extension studies are of dubious interpretation (and more when they refer to small effects and in this case were other Anti-Dementia drugs -donepezil- were used during the extension), the extension phase of study MRZ-9605 gives some evidence of a sustained effect of memantine over a period of 12 months.

MRZ-9403

This study is the early phase III trial which prompted the request of scientific advice to the CPMP in order to confirm the demonstrated efficacy which resulted in study MRZ-9605. As described above, study MRZ-9605 only confirmed the results in AD patients (and not in VAD patients) and use dda higher dose (20 mg/day).

Description of the study
Multicenter, double blind, randomised, placebo-controlled, parallel groups study designed to enrol approximately 168 patients.

The inclusion criteria were inpatients aged between 60 and 80 years with a predefined diagnosis of moderately severe to severe AD and VaD according to DSM-III, MMSE score <10, GDS stages 5-7, CGI-S 5-7 points and with a duration of dementia or symptoms >12 months.

Eventhough this study included patients suffering from AD or from VaD, only the AD patients are considered relevant for this application. It is important to note that the criterion for the AD group were prospectively defined in the statistical analysis plan, prior to breaking the treatment code. At the request of the CPMP, the results for the AD patients were presented separately, after the claim had been focussed to moderately severe to severe AD.

After an initial screening phase (and if indicated, wash-out phase of a minimum of two weeks), the patients were randomised to two parallel groups. A total of 167 patients were randomised to receive memantine tablet at a dose of 10 mg daily (although in the first week they received 5 mg) or placebo for 3 months.

Primary and secondary endpoints
Primary efficacy parameters were the clinical global impression of change (CGI-C) and a functional endpoint, the Rating Scale for Geriatric Patients (BGP), sub-scale "care-dependence". Among the secondary parameters were CGI-S, BGP total score and other scores, such as Modified D-Scale:G2 Scale and G2C-Scale ,and Instrumental Activities of Daily Living (IADL).

Statistical analysis
Nonparametric test (Fisher's exact test, Wilcoxon rank-sum test) on a confirmatory and descriptive level was used. The results described with ITT consist in the last observation carried forward (LOCF).

Results

Study populations/accountability of patients
Of the planned 168 patients, 167 were enrolled (82 with memantine and 84 with placebo,one patient died after randomisation without taking any trial medication). 166 patients were included in the ITT efficacy analysis and 151 were valid for PP(per protocol) analysis. Four memantine and four placebo patients prematurely terminated the trial (death was the cause of termination for all four).

Efficacy Results

Treatment differences between memantine and placebo patients were statistically significant for the prospectively defined primary efficacy variables assessed by CGI-C and by changes in BCG sub score "care dependency" taking effects of different trial centre's into account. Memantine resulted in a significantly higher percentage of improvement rates for the global endpoint (defined as any improvement in CGI-C) compared with placebo at both week 4 (59% vs 40%, p=0.006) and week 12 (73% vs 45% p<0.001, stratified Wilcoxon test). The same improvement rates for CGI-C with memantine (73% for both subsets) were observed in those patients with AD (Hachinski Ischaemic Scale [HIS] sum score <5 at baseline, n=79) and VaD (HIS ≥5 at baseline, n=87). Global endpoint response rates with memantine were slightly higher (77%) in patients with less severe degrees of care dependency (BGP care dependency sub score <20 points at baseline, n=75) compared with response rates (70%) in those with care dependency scores of ≥ 20 at baseline (n=91). Definition of subsets for this analysis was based on the HIS scores because for a minority of patients CT scans were not available.

Memantine was also significantly superior to placebo for the functional endpoint after 12 weeks of treatment (p = 0.016, stratified Wilcoxon test), despite a rather large placebo effect. In the memantine group, the mean BGP care dependency subscore (± standard deviation [SD]) fell from 21.3 ± 7.6 at baseline to 15.6 ± 8.8 by 12 weeks. In the placebo group the corresponding values were 21.8 ± 7.7 and 18.1 ± 9.4. 66% of memantine treated patients compared with 40% of placebo patients had clinically relevant (≥ 15% from baseline) improvements in BGP subscore.

The superiority of memantine treatment was also shown in a responder analysis using combined response criteria. Combined response for both primary efficacy criteria (improvement in CGI-C and ≥15% improvement in BGP) was observed in 61.3% of memantine treated patients compared with 31.6% of placebo treated patients.

Among the secondary parameters examined, a clinically relevant and statistically significant benefit for memantine compared with placebo was also observed in the BGP total score. In all items of the D-scale memantine patients performed better than placebo. This advantage was statistically significant ($p<0.05$) for the following items: ability to stand up, move, wash, take a bath or shower, dress, use toilet, group activities, and hobbies/interests. In this study a cognitive endpoint was not tested.

As confirmation of efficacy was only obtained for AD patients (study MRZ-9605 did not include VaD patients) the claimed indication was restricted to AD patients. After the claim had been focused to moderately severe to severe AD, the results for the AD patients were presented separately. Despite the relatively small sample size, an analysis of the effect of memantine in this group of AD patients (N=79) demonstrated statistically significant efficacy of memantine treatment in the three core domains as shown in the following table:

Table: Efficacy Results for the AD patients, MRZ-9403 (ITT population)

	ITT-LOCF analysis			ITT-OC analysis		
	Memantine (n=41)	Placebo (n=38)	p *	Memantine (n=39)	Placebo (n=37)	p *
BGP cognitive	-2.00	-1.03	0.007	-2.10	-1.05	0.004
CGI-C	3.15	3.47	0.002	3.08	3.46	0.005
BGP functional	-5.76	-2.79	0.003	-6.05	-2.89	0.002

*p-values are based on CMH test for raw means (using modified ridit score), controlling for centre.

Also in thissubset of AD patients, a responder analysis resulted in a statistically significant advantage for memantine over placebo. The criterion for response was: any improvement in the global rating (CGI-C) and >15% improvement in the Assessment Scale for Geriatric Patients (BGP) subscore care dependency. There were 61% (n=25) responders in the memantine group versus 26% (n=10) with placebo (p=0.003).

MRZ 9202

Description of the study
This study was conducted in population of vascular dementia patients and is therefore less relevant for the claimed indication in AD patients.

This phase III study was a comparative study of efficacy and tolerability of memantine versus placebo in patients suffering from probable vascular dementia (acc. NINDS-AIREN). The primary objective of this study was to determine the efficacy (assessed by ADAS-cog and CGI-C) of memantine in comparison with placebo. Tolerability and safety of memantine were also assessed. There was an initial placebo-controlled phase, followed by an open-label phase; one planned interim analysis. The number of patients planned was 545.579 were actually randomised, 464 completed the double-blind phase; 396 completed the open-label phase.

Male and postmenopausal female outpatients or day-care patients aged ≥50 years with an onset of symptoms at least one year before randomisation were included. They had to have a diagnosis of probable vascular dementia (DSM-III-R, NINDS-AIREN, Hachinski's Ischaemic Score modified by Rosen ≥4, CT/MRI), the severity of which was assessed as mild to moderate (DSM-III-R, MMSE ≥10 and <23). Depressive pseudodementia (HAM-D ≥18) as well as other secondary forms of dementia were excluded using CT, laboratory parameters, physical and neurological examination and medical history.

Memantine-HCl tablets were administered orally with a gradual dose increase to 20 mg/day over the first 3 weeks (dose titration: 5 - 10 - 15 - 20 mg/day), twice daily b.i.d. The treatment regimen was: Run-in phase (placebo single blind) for two weeks, followed by a double-blind phase (memantine tablets 2 x 10 mg/day versus placebo for 28 weeks), and an open-label phase (memantine tablets 2 x 10 mg/day for 24 weeks).

Primary and secondary endpoints
Primary efficacy was evaluated during the double-blind phase using the variables, ADAS-cog and CGI-C. Secondary variables were GBS, NOSGER and MMSE. During the open-label phase efficacy was evaluated by ADAS-cog, CGI-C, GBS, NOSGER and MMSE. Tolerability/Safety was evaluated by adverse events, standard laboratory values and ophthalmologic assessments.

Statistical analysis
Nonparametric confirmatory statistical tests for primary criteria were applied: for ADAS-cog Wilcoxon-Mann Whitney U test, and for CGI-C, χ^2 or Fisher exact test.

Results

In the confirmatory analysis, ADAS-cog was statistically significant in favour of memantine. However, CGI-C did not show any statistically significant difference between the groups. In the pooled ITT sample (i.e., samples before and after interim analyses combined), memantine resulted in a better ADAS-cog change from baseline (i.e., by a mean of 1.75 points [median 2 points]) than placebo. Improvement of cognitive performance relative to placebo was more pronounced in the subgroup of patients with low MMSE scores at baseline, and in those without macrolesions (usually infarctions) in their CT/MRI scans. For the secondary efficacy parameters (MMSE, NOSGER, GBS), there were a number of advantages in favour of memantine, which reached statistical significance (p=0.02) for the NOSGER dimension memory.

MRZ 9408

Description of the study
This study was conducted in population of vascular dementia patients and is therefore less relevant for the claimed indication in AD patients.

The phase III study was a comparative trial investigating efficacy and tolerability of memantine versus placebo in patients suffering from probable vascular dementia acc. NINDS-AIREN. There were 403 patients screened with 321 patients randomised of which 171 patients entered an open label period.

Male and postmenopausal female outpatients ≥ 60 years with an onset of symptoms of at least 6 months prior to randomisation were included. Subjects had to have a dignosis of probable vascular dementia (DSM-III-R, NINDS-AIREN) with a Modified Ischemic Scale (MIS) ≤ 5 and a recent CT scan (or MRI). Severity should be mild to moderate (DSM-III-R, MMSE ≥ 12 and ≤ 20). Depressive pseudodementia was excluded (HAM-D ≥ 15 points) as were other secondary types of dementia by CT, laboratory parameters, physical examination, neurological examination and medical history.

Memantine HCl tablets were administered 2 x 10 mg/day, per o.s. (Gradual dose increase during Weeks 1-3). The treatment regimen was as follows: Week – 2 to baseline (Day 0) a placebo run-in period; Week 1 to week 28 a double blind treatment period and from Week 29 on (still ongoing) memantine (open label period).

Primary and secondary endpoints
Evaluation of primary efficacy was made by ADAS-Cog and dichotomised CIBIC-Plus (independent rater). Secondary efficacy variables were ADAS-Noncog, GBS, CGI-C (physician), CGI-C (caregiver), NOSGER, MMSE, CIBIC-Plus, ADAS-cog. Safety was evaluated by assessment of adverse events, standard laboratory values at week 0, 12, 28, 38 and 51, ECG, vital signs and physical examination (week –2 and 28).

Results

In summary the confirmatory CIBIC-plus analysis was in favour of memantine (at visit 7- week 28) but did not reach statistical significance. Due to the hierarchical testing procedure of the protocol, confirmatory testing for ADAS-cog was not performed. On the ADAS-cog total score, memantine patients improved by 0.4 (mean), while the placebo group worsened by 1.6 points (exploratory analysis p = 0.01, ITT, LOCF replacement). Among the secondary efficacy parameters, which were analysed in the TPP subset, CGI-C ratings (trichotomised and raw values) of the investigators were statistically significant in favour of memantine. In addition, there was a statistically significant treatment effect for the MMSEtotal score with a difference between groups of 1.7 points in favour of memantine (p = 0.003), and for the sub-score "Intellectual Function" of the GBS. A sub-group analysis of the ADAS-cog results by MMSE baseline strata, while resulting in an advantage for the memantine treatment group in all subsets, showed the best treatment result for memantine in the subset of patients with low MMSE scores <15.

Discussion on clinical efficacy

The requested indication was restricted to treatment of patients with moderately severe to severe Alzheimer's disease. Memantine is not proposed any more for vascular dementia for which the submitted evidence was clearly insufficient. The studies in VaD patients (MRZ- 9408 and MRZ-9202) did not include patients that reflected the claimed indication. They were patients with less severity than those proposed to be treated. A reanalysis so as to study as a subgroup the patients towards the "moderately severe" end of the included patients was performed but this can not be considered as sufficient evidence. In addition the suitability of the ADAS-cog (Alzheimer Disease Assessment Scale) score for patients with vascular dementia remains in doubt. Also there is no confirmatory well designed trial for VaD patients as it is the case for AD patients

The pivotal trial MRZ 9605 was conducted in a patient population with a moderately severe to severe AD, which was adequately defined in terms of diagnostic criteria and the proposed dose of 20 mg/day was used. The duration of follow-up (6 months with an open extension) is acceptable to evaluate efficacy in a chronic situation. As it is consensual nowadays the primary end-points were double involving 2 domains: global and functional. The trial also included a pre-specified analysis of responders. 252 patients were randomised and 181 completed the study. The discontinuation rate was higher in the placebo group 33% vs. 23% in the memantine group.

Of the two well-chosen primary variables (Modified ADCS-ADL css Inventory and CIBIC plus) only the functional one (ADCS-ADL css Inventory) reached statistically significant difference (p=0.0217) while the global one (CIBIC plus) only showed a strong trend (p=0.064). A reanalysis shows that when the CPMP Guideline *Points to Consider on Missing Data (CPMP/EWP/1776/99 draft)* is used (Observed cases/OC instead of the pre-established LOCF) the borderline statistical significance (p=0.064) becomes full significance (p=0.025). No cognitive variable was considered as primary at the suggestion of a previous scientific advice of the CPMP on the basis that cognition would be difficult to assess in such advanced demented patients and that minor cognitive changes would be inconsequential unless they translated into global and functional improvements. It was considered as a secondary endpoint (SIB) and it obtained statistically significant results (p=0.0003, LOCF) in favour of memantine. In addition, when a "responder" analysis was performed, statistical significance was reached in one of the two pre-established definitions of responder used. The applicant provides a further (post hoc) definition (related to responses in both cognitive and global end-points) which is also positive for memantine. This definition of responder is similar but not the same as that used during the CPMP assessment of Rivastigmine for the treatment of mild to moderate AD.

The results of the extension phase of study MRZ-9605 show some apparent improvement in the deterioration rate (on both primary variables and SIB) of those patients on placebo that, after the end of the blinded phase, are switched to memantine so that their status approaches, over the weeks, the status of the patients continuing on memantine. Although open label extension studies are of dubious interpretation (and more when they refer to small effects), the extension phase of study MRZ-9605 substantiates the sustained efficacy of memantine over a treatment period of 12 months.

In addition other antidementia drugs (donepezil) were used during the extension phase further complicating the interpretation of the results.

Study MRZ 9403 included vascular dementia patients but the 79 Alzheimer's disease patients included seem to have been adequately pre-classified and in them memantine was better than placebo in both primary endpoints (functional and global)although only half the proposed dose was used and that it only lasted for three months. However, the statistically significant and consistent results favouring memantine provide supportive evidence of the efficacy of memantine in AD patients.

Clinical safety

Patient exposure:

The safety database for memantine covers 32 completed studies in various indications which included 3249 subjects, of whom 2863 provide safety data (386 patients withdrew prior to any drug exposure). Of the 2863 patients in the safety population of the Integrated safety summary (ISS), 227 were healthy volunteers from pharmacokinetic and pharmacodynamic studies, 2231 were patients fromfromclinical studies in dementia/dementia syndrome, 587 of whom had moderately severe to severe AD and VaD, 205 were patients with Parkinson's disease and 200 were patients with spasticity. The overall population consisted of 54% female, 45% male, with median age of 74 years (range 18-97). A total of 1943 subjects received memantine, 1158 placebo (counting 250 individuals in both the memantine and placebo group as they received both agents), and 12 baclofen (not discussed in this report). Median exposure to memantine was 90 days, to placebo 84 days (memantine range 1-570, placebo range 1-241). A total of 1545 memantine patients were treated with the recommended dose (20 mg per day), with 360 receiving doses above the recommended level.

Adverse events and serious adverse event/deaths:

The overall frequency of patients who experienced AEs, irrespective of relationship to study medication was similar with memantine (n=922 out of 1717; 54%) compared with placebo (n=624 out of 1158; 54%). The majority of AEs were mild to moderate in intensity.

Most frequent AEs with memantine vs placebo irrespective of relationship to study medication (≥3% on memantine) in all studies were as follows:

Preferred term (WHO ART)	Memantine, n=1717	Placebo, n=1158
Dizziness	174 (10%)	66 (6%)
Headache	129 (8%)	40 (4%)
Fatigue	114 (7%)	47 (4%)
Agitation	100 (6%)	110 (10%)
Somnolence	86 (5%)	54 (5%)
Confusion	76 (4%)	73 (6%)
Constipation	62 (4%)	44 (4%)
Diarrhoea	48 (3%)	39 (3%)
Sleep disorder	45 (3%)	46 (4%)
Nausea	44 (3%)	28 (2%)

On the whole, 195 (11%) memantine patients and 110(10%) placebo patients experienced AEs that lead to discontinuation of therapy. Dizziness was the most common reason for discontinuation of memantine (2% vs 1% for placebo). All other AEs leading to discontinuation occurred in less than or equal to 1% of patients with no particular pattern of type of AE between groups.

The most frequent AEs assessed as attributable to study drug (ADRs) were dizziness (7% vs 2%), headache (5% vs 2%) and fatigue/tiredness (4% vs 1%). Agitation occurred less with memantine than with placebo (6% vs 10%).

In patients with moderately severe to severe dementia, the overall frequency of AEs irrespective of relationship to medication was similar with memantine compared with placebo (65.2% vs 65.6%). In this target population, the most frequent adverse events were similar to the overall population (all studies) in the Integrated Safety Summary database. Although relatively uncommon in both groups, a slightly higher frequency of hallucinations (all of them "mild to moderate") was observed with memantine (5% vs 2% on placebo) and a lower frequency of agitation was observed with memantine vs placebo, in keeping with the observation in the overall safety population treated with memantine.

Most frequent AEs with ≥ 3% on memantine vs placebo irrespective of relationship to study medication, patients with moderately severe to severe dementia (Patients with MMSE < 15 at baseline, including VaD patients):

Preferred term (WHO ART)	Memantine n=299	Placebo n=288
Agitation	27 (9.0%)	50 (17.4%)
Inflicted Injury	20 (6.7%)	20 (6.9%)
Urinary Incontinence	17 (5.7%)	21 (7.3%)
Diarrhoea	16 (5.4%)	14 (4.9%)
Insomnia	16 (5.4%)	14 (4.9%)
Dizziness	15 (5.0%)	8 (2.8%)
Headache	15 (5.0%)	9 (3.1%)
Hallucination	15 (5.0%)	6 (2.1%)
Fall	14 (4.7%)	14 (4.9%)
Constipation	12 (4.0%)	13 (4.5%)
Coughing	12 (4.0%)	17 (5.9%)
Bronchitis	11 (3.7%)	13 (4.5%)
Vomiting	11 (3.7%)	6 (2.1%)
Somnolence	10 (3.3%)	10 (3.5%)
Anorexia	10 (3.3%)	6 (2.1%)
Confusion	9 (3.0%)	9 (3.1%)
Urinary Tract Infection	9 (3.0%)	22 (7.6%)

The pattern of AEs assessed as at least possibly related to trial medication (adverse drug reactions, ADR) in patient with dementia for the application was similar to that observed for AEs irrespective of treatment relationship. The overall frequency of AEs for memantine (24%) was equal to placebo (25%). Agitation was the most frequent ADR, but again was less frequent with memantine (4%) than with placebo (8%). The AEs attributable to study drug (ADRs) occurring most commonly (> 1%) with memantine and being more frequent than with placebo were hallucination (2.0 vs 0.7%), dizziness (1.7 vs 1.0%), headache (1.7 vs 1.4%), confusion (1.3 vs 0.3%), and fatigue/tiredness (1.0 vs 0.3%). Further uncommon ADRs were: anxiety, cystitis, hypertonia, increased libido and vomiting. There were no major differences in the frequency of serious adverse events (SAEs) between memantine and placebo.

The safety database does not list any signs or symptoms of withdrawal after discontinuation of memantine treatment. This is in line with the relatively long half-life of the compound. The majority of AEs occurred more commonly at the beginning of treatment, with 9% of memantine treated patients compared with 6% of placebo treated patients experiencing at least one AE on Day 1 of therapy, with a cumulative 3-month incidence showing a similar frequency of AEs with memantine and placebo (48% and 45% respectively).

The overall incidence of AEs increased with age in both the memantine and placebo groups with no suggestion of any age-related tolerability issues with memantine. If anything, tolerability of memantine compared with placebo appeared to be better in patients >65 years, which may in part reflect poor tolerability of higher than recommended doses in short lived phase I trials involving younger subjects. There were no relevant gender differences in tolerability.

Serious Adverse events
There were no major differences in the frequency of SAEs between memantine and placebo, with 125 (7%) memantine treated patients and 112 (10%) placebo treated patients who experienced a SAEs. The majority of SAEs were assessed as unrelated to study medication, with 38 (2%) on memantine and 13 (1%) on placebo assessed as at least possibly related to treatment. There were no obvious differences between the groups in type of SAEs.

Deaths
A total of 41 (2%) patients on memantine and 16 (1%) on placebo died during the programme, with no major differences in cause of death between groups. The applicant explains the slightly higher rate of death for memantine patients by a relatively high mortality in one nursing home trial (MRZ-9406) in which all patients received memantine. In placebo-controlled trials, the mortality rates overall were similar to placebo.

Laboratory findings

There were no clinically relevant differences in haematological or biochemical parameters between memantine and placebo patients. The incidence of laboratory findings reported, as AEs was low in both groups (4% in memantine and 6% in placebo). There were no important differences in vital signs or ECG changes for memantine compared with placebo.

Post-marketing experience, phase IV

Post-marketing safety experience is available from the German market. More than 100 million daily doses of memantine have been sold. Overall, the applicant received spontaneous reports of 73 events in 48 patients. The following events were reported in more than one patient: nervousness (6), convulsions (4), tremor (3), aggressive reaction (3), circulatory failure (2), hypertension (2), dizziness (2), dyskinesia (2), nausea (2), menstrual disorder (2), bullous eruption (2), pruritus (2).

In addition, 2 post marketing surveillance studies of memantine in "dementia syndrome" have been performed in Germany. In the first (MRZ-9002), 1420 patients with dementia syndrome were followed during treatment with memantine, usually at doses of 10-20 mg per day, for more than one year. The most frequently reported AEs were restlessness (1.3%), nausea (0.9%), dizziness (0.8%) and fatigue/tiredness or sleep disorders (0.4%). In the second post-marketing surveillance (MRZ-9303), 531 care-dependent patients were treated with memantine up to 30 mg per day for a mean of 44 days. Memantine was well tolerated, n=16 (3%) patients reported AEs, with restlessness being the most frequent symptom.

- **Discussion on clinical safety**

The product has been on the market for nearly twenty years in a European country without apparent cause for concern, which can be considered as giving some reassurance. In addition there has been clinical exposure in the older clinical trials.

The most frequent adverse events reported with memantine have been dizziness, followed by headache and fatigue. Agitation occurred less with memantine than with placebo. There is no suggestion of a psychedelic effect that could be feared as a result of activation of the NMDA receptors. Even if the target population would have had difficulties in reporting this kind of effects the fact that the levels of agitation were decreased is in favour of absence of such theoretical psychedelic effects.

Despite the absence of studies formally addressing the question of withdrawal and dependence, there are no signals in the data available suggesting its existence. Taking into account the indication granted, the clinical evidence available gives reassurance of a sufficient safety profile.

Considering the still pending preclinical issues, the company commits to perform a long term safety monitoring of ocular, neurotoxic and pulmonar side-effects. The company also proposes to perform new clinical studies of a longer duration and with higher doses than those proposed currently in patients with glaucoma, neuropathic pain and mild to moderate AD.

5. Overall conclusion and benefit/risk assessment

- **Quality**

The important quality characteristics of memantine film-coated tablets and oral drops solution are well-defined and controlled, and the products are formulated, manufactured and controlled in a way that is characteristic of each product. The specifications and batch analytical results indicate consistent products, which in turn indicates uniform clinical performance from batch to batch. There are no outstanding quality issues, which would have a negative impact on the benefit/risk balance.

- **Preclinical pharmacology and toxicology**

Overall, the primary pharmacodynamic studies provided adequate evidence that memantine acts as a non-competitive antagonist of the NMDA receptors. In the general pharmacology studies, the major observed sign was ataxia preceded by increased locomotor activity. The target organ producing limiting toxicity is the brain. Major observed effect was ataxia and at highest doses seizures and respiratory arrest were observed.

Neuronal vacuoles (not related to Olney lesions) in the central nervous system were seen, at lethal dose levels in the 13-week dietary mouse study. The repeated dose toxicology programme revealed an increased prevalence of pulmonary foamy macrophages at high doses of memantine and electron microscopic examination of the eye tissues showed findings of abnormal lysosomal storage (granules) in ganglion cells and in pigment epithelium cells only. Most of these findings are suggested to be species-specific and/or to appear at doses well in excess of the therapeutic dose. Exposure data for these findings were scarce and safety margin has been calculated mainly from administered dose. Although it is a limitation, the post marketing experience for memantine for decades in a European country with no special safety concerns has also been taken into account. The Company are already in the process of conducting extensive clinical trials where relevant long-term safety data will be collected. They commit to provide on an annual basis the CPMP with safety analysis of two large placebo-controlled studies in glaucoma patients, neuropathic pain and non-severe Alzheimer's disease patients.

- **Efficacy**

The indication finally requested is: treatment of patients with moderately severe to severe Alzheimer’s disease.

The pivotal trial MRZ-9605 was conducted in a patient population with moderately severe to severe AD, which was adequately defined by the diagnostic criteria used. The duration (6 months followed by an open extension phase) is acceptable to evaluate efficacy in a chronic situation.

For the indication moderately severe to severe AD, clinical efficacy is documented by MRZ-9605 and the AD patients in MRZ-9403 in functional (ADL) and clinical global impression of change as well as cognitive domains. Responder analyses in both studies showed a higher rate of responders for memantine than for placebo.

The extension phase of study MRZ-9605 gives some evidence of a sustained effect of memantine over a treatment period of 12 months. Additionally, study MRZ-9605 reported a positive effect on activities of daily living, which appears to transfer into measurable benefits in caregiver time as well as a reduction in the number of institutionalisations.

- **Safety**

The product has been on the market for nearly twenty years in a European country without apparent cause for concern, which can be considered as giving some reassurance. In addition there has been clinical exposure in the older clinical trials.

In clinical trials the most frequent adverse events reported with memantine have been dizziness, followed by headache and fatigue. Agitation occurred less with memantine than with placebo. There is no suggestion of a psychedelic effect that could be feared as a result of activation of the NMDA receptors. Even if the target population would have had difficulties in reporting this kind of effectsthe fact that the levels of agitation were decreased is in favour of absence of such theoretical psychedelic effects. Despite the absence of studies formally addressing the question of withdrawal and dependence, there are no signals in the data available suggesting its existence. Taking into account the indication granted, the clinical evidence available gives reassurance of a sufficient safety profile.

Considering the still pending preclinical issues, the company are already in the process of conducting extensive clinical trials where relevant long-term safety data will be collected. In some of them higher doses than those now approved will be used. These studies will enroll patients with glaucoma, neuropathic pain and milder forms of AD.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of Axura in the treatment of moderately severe to severe Alzheimer's disease is favourable.