London, 18 October 2012
EMA/17269/2013
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Memantine FGK

International nonproprietary name: memantine hydrochloride

Procedure No. EMEA/H/C/002687

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjugation with the "Question and Answer" document on withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	**Memantine FGK**
INN (or common name) of the active substance(s):	Memantine
Applicant:	FGK Representative Service GmbH
Applied Indication(s):	Treatment of patients with moderate to severe Alzheimer's disease
Pharmaco-therapeutic group (ATC Code):	Other Anti-dementia drugs (N06DX01)

1. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Rapporteur considers that the application for Memantine FGK, in the treatment of patients with moderate to severe Alzheimer's disease, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

1. Though a statistically significant difference was seen on the co- primary endpoint, the difference was small, whereas the effect on the secondary endpoint, ADL, was not statistically significant. Therefore the clinical relevance of the effects are doubtful and may not outweigh the risk. The company should justify the benefit/risk is positive even the more so as a comparison with the immediate release form is lacking.
2. By only one placebo-controlled study a clearcut comparison of efficacy and safety of once daily Memantine FGK with the memantine IR 20 mg dose on the market was not possible at present. The choice of a dosis of 28 mg once daily should be better justified (major objection).
3. Discussion on the R/B is hampered by the lack of direct comparison to memantine IR making it impossible to place on the R/B balance of the ER product in to perspective. It would have been expected to have the result of a head-to-head study comparing efficacy and safety of the IR and the ER forms in patients with Alzheimer's disease including the comparison of the PK profile of the ER formulation with the IR formulation administered 20 mg once daily. The applicant should justify the absence of such data.

Proposal for inspection

GMP inspection(s)

None

GCP inspection(s)

None

New active substance status

Based on the review of the data the Rapporteur considers that the active substance memantine hydrochloride contained in the medicinal product Memantine FGK is not to be qualified as a new active substance in itself.

2. EXECUTIVE SUMMARY

2.1. Problem statement

Memantine was approved in the EU under the trade name Axura for the treatment of patients with moderately severe to severe Alzheimer's disease on May 17, 2002.

Memantine (l-amino-3,5,-dimethyladamantane hydrochloride) is a moderate affinity, uncompetitive (open-channel) N-methyl-D-aspartate (NMDA) receptor antagonist that binds preferentially to the NMDA-receptor–operated cation channels in a use-dependent and voltage-dependent manner with rapid blocking/unblocking kinetics.

Memantine, as an NMDA receptor antagonist, is thought to exert its effect by inhibiting the excitotoxic effects of the excitatory amino acid glutamate.

FGK representative Service GmbH applies for a MAA for Memantine FGK submitted as a hybrid application according to Article 10(3) of Directive 2011/83/EC. Memantine FGK formulation differs from the reference product Axura in strengths and in pharmaceutical form.

The application relies in part on the results of pre-clinical tests and clinical trials for the reference product Axura film-coated tablets and in part on new data.

The reference product for Memantine FGK is Axura, an immediate-release (IR) tablet formulation that was approved at a dosage of 10 mg twice daily (BID) by the European Medicines Agency (EMA) on May 17, 2002 for the treatment of moderately severe to severe dementia of the Alzheimer's type. In November 15, 2005, the indication of Axura was extended to the treatment of moderate to severe Alzheimer's disease. Based on the fact that pharmacokinetic data in healthy volunteers showed minimal differences in the plasma concentration-time profile between twice-daily and once-daily dosing regimen, the recommended posology was changed on May 8, 2008 from twice-daily 10 mg to once daily 20 mg.

2.2. About the product

Memantine FGK, the drug under application, was developed with the objective of providing a once daily formulation with a slower absorption rate and a higher systemic exposure than those provided by the IR tablet.

The therapeutic indication for Memantine FGK will follow the approved indication of the reference product Axura, i.e. "treatment of moderate to severe Alzheimer's disease".

The following table compares Memantine FGK versus the reference medicinal product Axura film-coated tablets:

	Memantine FGK	**Axura®**
Active Substance	Memantine hydrochloride	Memantine hydrochloride
Pharmaceutical form	Prolonged-release capsule, hard	Film-coated tablets
Strengths	7 mg, 14 mg, 21 mg, 28 mg	5 mg, 10 mg, 15 mg, 20 mg
Therapeutic indication	Treatment of patients with moderate to severe Alzheimer's disease.	Treatment of patients with moderate to severe Alzheimer's disease.
Route of administration	Oral use	Oral use

2.3. The development programme/compliance with CHMP guidance/scientific advice

N/A

2.4. General comments on compliance with GMP, GLP, GCP

GCP

As sponsor of the application for the marketing authorisation of memantine FGK, FGK Representative Service GmbH mentions that the clinical trials carried out outside the European Union meet ethical requirements of Directive 2001/20/EC and were performed in compliance with the ICH Guideline E6 for Good Clinical Practice. Studies outside the EU were performed in the US, Argentina, Mexico and Chile.

2.5. Type of application and other comments on the submitted dossier

- Legal basis:

Memantine was approved in the EU under the trade name Axura for the treatment of patients with moderately severe to severe Alzheimer's disease on 17May, 2002. The approved dosage was 10 mg twice daily. On 15 November, 2005, the indication of the reference medicinal product Axura was extended to the treatment of moderate to severe Alzheimer's disease. Based on the fact that pharmacokinetic data in healthy volunteers showed minimal differences in the plasma concentration-time profile between twice-daily and once-daily dosing regimen, the recommended posology was changed on May 8, 2008 from twice-daily 10 mg to once daily 20 mg.

Memantine FGK formulation differs from the reference product Axura in strengths and in pharmaceutical form. A hybrid application (Article 10(3) of Directive 2001/83/EEC) is therefore submitted for the MAA for Memantine-FGK and results of pre-clinical and clinical trials are provided, in addition to the supportive bioavailability/bioequivalence/PK studies.

A Pre-submission Meeting with the EMA was scheduled the 25th of April and the validity of a hybrid application for Memantine-FGK was discussed in this meeting. From a legal perspective, EMA finally confirmed that a hybrid marketing authorisation application was appropriate and valid in the case of the product under application Memantine FGK capsules. The reference product chosen by the applicant, Axura film-coated tablets, is authorised within the EU via the centralised procedure based on a full dossier and is therefore acceptable, keeping in mind that bioequivalence is not claimed by the applicant and that the PK results provided with the reference product are only supportive data.

- Accelerated procedure: NA
- Conditional approval: NA
- Exceptional circumstances: NA
- Biosimilar application: NA
- 1 year data exclusivity: NA
- Significance of paediatric studies: NA

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Introduction

Memantine FGK formulation differs from the reference product Axura in strengths and in pharmaceutical form. A hybrid application is therefore submitted for the MAA for Memantine-FGK and results of pre-clinical and clinical trials are provided, in addition to the supportive bioavailability/bioequivalence/PK studies.

3.2. Quality aspects

Drug substance

Memantine hydrochloride is supplied by two different manufacturers

The drug substance is a white crystalline powder. It is highly soluble in water and shows no optical rotation. Only one crystalline form has been observed so far. The potential impurities originating from starting materials, isomers, by-products of synthesis, residual solvents and inorganic impurities are discussed. The drug substance specifications include tests for description, solubility, identification (IR, chloride), loss on drying, sulphated ash, heavy metals, clarity and colour of solution, related substances (GC), residual solvents (GC) and assay (GC). Validation data are presented for the in-house analytical methods. Batch analysis data are presented on six batches from manufacturing site. The proposed re-test date is 60 months when stored in double LDPE bags placed in fibre drum or HDPE drum.

Drug product

Memantine FGK prolonged-release capsules, hard 7 mg, 14 mg, 21 mg and 28 mg are for oral use. The capsules are packaged in PVC-aluminium blisters. The formulation contains the following excipients: sugar spheres, Povidone, talc, OpadryClear seal coating and gelatin capsule shell. The drug product is developed as a prolonged-release formulation since it allows flexibility in dosing and reduces the side effects associated with immediate release formulations. The dissolution profiles of the different strengths are similar.

The drug product is controlled for description, identification (GC, HPLC), assay (HPLC), degradation products (GC), content uniformity (Ph. Eur. 2.9.40), dissolution (Ph. Eur. 2.9.3) and microbial limits (Ph. Eur. 2.6.12, 2.6.13). Validation data are presented for the in-house analytical methods. Batch analysis data are presented on three batches of each capsule strength that were manufactured from three bulk batches. A short discussion is presented on the potential impurities found during manufacture and stability studies.

The materials used for the container closure system comply with relevant EU food legislation relating to plastic materials coming into contact with foodstuffs and the PVC materials additionally conforms to Ph. Eur. requirements.

The proposed shelf life is 36 months when stored below 30°C.

Discussion on chemical, pharmaceutical and biological aspects

Drug substance

The general information is appropriately described.

The manufacturing processes from both manufacturers is appropriately described but some issues are raised in the restricted part of the ASMF. The discussion regarding impurity profile is acceptable. However, potential genotoxic impurities should be discussed as well as a potential residual organic solvent.

Overall, the proposed specifications are suitable to control the quality of memantine hydrochloride. They comply with the ICH requirements and with Ph. Eur. general monograph “Substances for Pharmaceutical use”.

The analytical methods are satisfactorily described and suitable for their intended use.

Drug product

The drug product composition is not appropriately described. It should include the qualitative and quantitative composition of the compound excipients used and additional corrections need to be done.

The choice of the formulation, manufacturing process and container closure system are documented in the pharmaceutical development section. A few issues need to be addressed such as a discussion of the dissolution profiles across the physiological pH range and the discrepancies with respect to the theoretical amount of release modifying polymer.

The responsibilities of the sites involved in manufacture, testing and release are defined and covered by Manufacturing Licenses and/or GMP certificates. The batches size proposed for routine manufacture should be confirmed. The manufacturing process and in-process controls for the manufacture of commercial batches are insufficiently described. The presented in-process controls include only a few product-related characteristics. A number of issues are therefore asked.

The selected excipients are in compliance with the Ph. Eur. requirements or are composed of excipients that comply with their relevant Ph. Eur. monograph. The specifications for gelatin capsules are inappropriately described. The valid analytical reference for colouring stuff should be stated. Relevant statements regarding residual solvents in excipients are missing. Some other minor issues need to be addressed.

The shelf life specifications are not presented in section P.5. At the time of the stability studies shelf life specifications differed for a number of tests. If any difference occurs between the release specifications and shelf life specifications for testing of future stability batches, these should be appropriately justified. The in-house analytical methodology is appropriately described, yet a number of validation parameters are not covered or their evaluation is based on a previous formulation for which the validation report is not presented. All relevant validation data should be presented.

The container closure system is appropriately described.

The stability studies are performed in accordance with ICH stability guidelines on Memantine FGK prolonged-release capsules packaged in the blisters proposed for marketing. It is still to be confirmed whether these primary stability batches are representative with respect to the process variables and equipment used (reference is made to part P.3 Manufacture). The proposed bracketing design is justified since the different capsule strengths are manufactured by different fill amount of the same prolonged-release beads. The overall stability results show that the drug product is stable and confirm the findings of the excellent stability of the drug substance memantine hydrochloride. A shelf life of 36 months when stored below 30°C is appropriate. Still, stability data from commercial batches are asked that are manufactured with the proposed theoretical polymer weight gain. It is also asked to include the additional labeling statement ‘store in the original package in order to protect from moisture’ since it cannot be excluded that elevated humidity contributes to color fading of the capsules. Additional confirmation is asked that ‘microbial testing’ will be performed on the commercial batches at the end of stability studies.

Conclusions on the chemical, pharmaceutical and biological aspects

The provided chemical data are acceptable provided the applicant submits satisfactory responses to the preliminary list of questions.

3.3. Non clinical aspects

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on up-to-date and adequate scientific literature and the EPAR for Axura. No specific non-clinical studies were

performed for the given formulation. This is considered acceptable taking into account that the pharmacokinetic and safety aspects have been addressed from a clinical point of view and taking into account that the non-clinical and clinical profile of IR memantine is well-known.

Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Memantine FGK is considered unlikely to result in any significant increase in the combined sales volumes for all memantine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

3.4. Clinical aspects

Tabular overview of clinical studies

Table 2: Summary of clinical studies

Protocol Number: Title *Centre(s)*	*Study Design*	*Treatment Administered*	*Number Treated (Number per Group)*	*Treatment Duration*	*Age Range, y (Mean)*	*Number Male/ Female Subjects*
GROUP 1 STUDIES **PLACEBO-CONTROLLED STUDY IN MODERATE TO SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE (Group 1A)**						
MEM-MD-50: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type 38 study centres in the United States, 23 in Argentina, 11 in Chile, and 11 in Mexico	Multinational, multicentre, randomized, double-blind, placebo controlled, parallel group	Placebo Memantine ER 7-mg capsules administered orally once daily; dosage titrated to 28 mg/d	676 (335 placebo/ 341 memantine)	26 weeks (1 to 2 weeks placebo, 24 weeks memantine)	49-97 (76.5)	189 M/ 487 F
OPEN-LABEL STUDIES IN MODERATE TO SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE (Group 1B)						
MEM-MD-51: An Open-Label Evaluation of the Safety of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type 31 study centres in the United States	Multicentre, open label	Memantine ER 7-mg capsules administered orally once daily; dosage titrated to 28 mg/d or Memantine ER 28-mg capsules administered orally once daily	164	52 weeks	52-93 (77.5)	62 M/ 102 F
MEM-MD-54: An Open-Label Extension Study Evaluating the Safety and Tolerability of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type 26 study centres in the United States, 23 in Argentina, 9 in Chile, and 8 in Mexico	Multinational, multicentre, open-label, extension study	Memantine ER 7-mg capsules administered orally once daily; dosage titrated to 28 mg/d	491 (245 placebo/ memantine, 246 memantine/ memantine)	28 weeks	50-93 (76)	139 M/ 352 F
OPEN-LABEL LONG-TERM STUDY IN MODERATE TO SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE (Group 1S)						
MEM-MD-82: An Open-Label Extension Study Evaluating the Safety of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type 24 study centres in the United States	Open-label, multicentre, extension study	Memantine ER 28-mg capsules administered orally once daily; total dosage 28 mg/d	66 (46 from MEM-MD-51, 20 from MEM-MD-54)	52 weeks	52-89 (75)	27 M/ 39 F

Protocol Number: Title *Centre(s)*	*Study Design*	*Treatment Administered*	*Number Treated (Number per Group)*	*Treatment Duration*	*Age Range, y (Mean)*	*Number Male/ Female Subjects*
GROUP 2 STUDIES **PLACEBO-CONTROLLED STUDIES IN NEUROPATHIC PAIN**						
MEM-MD-06A Double-blind Comparison of Memantine and Placebo in the Treatment of Chronic Pain in Patients with Diabetic Neuropathy 32 centres in the United States	Multicentre, randomized, double-blind, parallel group, flexible dose	Placebo Memantine IR 5-mg tablets administered orally twice daily; dosage started at 10 mg/d and titrated to 40 mg/d over first 4 weeks	525 (266 placebo/ 259 memantine)	17 weeks (1 week placebo, 16 weeks memantine)	25-84 (60.5)	314 M/ 211 F
MEM-MD-19 Randomized, Double-blind, Placebo-Controlled, Flexible-Dose Study of the Efficacy and Safety of Memantine in Comparison to Gabapentin in Patients with Painful Diabetic Neuropathy 18 centres in the United States	Multicentre, randomized, double-blind, placebo controlled, parallel group, flexible dose	Placebo Gabapentin 300- and 400-mg capsules administered orally Memantine IR 5-, 10-, and 20-mg tablets; dosage started at 10 mg/d and escalated to 60 mg/d over first 5 weeks of double-blind treatment	158 (52 placebo, 55 gabapentin, 51 memantine)	18 weeks (1 week placebo, 17 weeks memantine)	20-82 (57.5)	91 M/ 67 F
MEM-MD-20 A Randomized, Double-blind, Placebo-Controlled, Flexible-Dose Study of the Efficacy and Safety of Memantine in Comparison with Gabapentin in Patients with Postherpetic Neuralgia. 22 centres in the United States	Multicentre, randomized, double-blind, placebo controlled, flexible dose	Placebo Gabapentin 300- and 400-mg capsules administered orally; maximum dosage of 2400 mg/d Memantine IR 5-, 10-, and 20-mg encapsulated tablets; dosage started at 10 mg/d and escalated to 60 mg/d over first 5 weeks of double-blind treatment	145 (46 placebo, 48 gabapentin, 51 memantine)	18 weeks (1 week placebo, 17 weeks memantine)	20-82 (64.2)	67 M/ 78 F
GROUP 2 STUDIES **NON–PLACEBO-CONTROLLED STUDIES IN NEUROPATHIC PAIN**						
MEM-MD-06B Open-Label Extension of Memantine Treatment in Patients with Painful Diabetic Neuropathy 32 centres in the United States	Multicentre, open-label extension study	Memantine IR 5-mg tablets administered orally; dosage started at 10 mg/d and titrated to 40 mg/d over first 4 weeks	393 (210 placebo/ memantine, 183 memantine/ memantine)	40 weeks	30-80 (60.4)	238 M/ 155 F
MEM-MD-06C A Randomized, Double-blind, Fixed-Dose Study Comparing the Efficacy and Safety of Daily Doses of 40 mg, 60 mg, and 80 mg of Memantine in Patients with Painful Diabetic Neuropathy 16 study centres in the United States (randomized patients)	Multicentre, randomized, double-blind, parallel-group, fixed-dose, extension study	Memantine IR 10-mg tablets administered orally; dosages of 40. 60, or 80 mg/d	79 (40-mg: 28, 60-mg: 25, 80-mg: 26)	16 weeks	34-78 (58.4)	47 M/ 32 F
OPEN-LABEL STUDY IN BIPOLAR DISORDER						
MEM-MD-27 A Pilot Evaluation of the Safety and Efficacy of Memantine in Patients with Acute Mania Associated with Bipolar I Disorder 5 study centres in the United States	Multicentre, open label, cohort sequential, dose escalation, inpatient	Memantine IR 10-mg tablets administered orally; dosage 20 to 50 mg/d, Cohort 1: targeted dosage of 20 to 30 mg/d; Cohort 2: targeted dosage of 20 to 40 mg/d Cohort 3: targeted dosage of 30 to 50 mg/d	35 (Cohort 1: 12, Cohort 2: 12, Cohort 3: 11)	3 weeks	18-66 (41.2)	16 M/ 19 F
MEM-PK-23: Evaluation of Memantine Pharmacokinetics Following Single- and Multiple-Dose Administration of a Memantine HCl-Extended-Release Capsule and Immediate-Release Tablet in Healthy Human Subjects 1 study centre in the United States	Single centre, randomized, open label, multiple dose, two-way crossover	Treatment A: memantine IR Day 1: one 10-mg tablet (fasted) Days 4-9: one 5-mg tablet BID Days 10-15: one 10-mg tablet (morning) and one 5-mg tablet (evening) daily Days 16-28: one 10-mg tablet BID Day 29: one 10-mg tablet BID (morning dose fasted) Treatment B: memantine ER Day 1: A single 28-mg capsule (fasted) Days 4-9: one 14-mg capsule daily Days 10-15: one 21-mg capsule daily Days 16-28: one 28-mg capsule daily Day 29: one 28-mg capsule (fasted)	26 (23/24)	54 days	19-44 (27.8)	15 M/11 F

Pharmacokinetics

Memantine FGK is intended for once-daily dosing using an initial titration scheme with 7, 14, and 21 mg once daily and then a once-daily dose of 28 mg as the recommended maintenance dose.

Memantine FGK was developed with the objective of providing a formulation with a slower absorption rate and a higher systemic exposure (higher dosage) than those provided by the IR tablet, without the associated increased risk of AEs.

Memantine is a well-known and well-characterised active substance. Due to this well established nature, the applicant has not conducted any distribution, hepatic metabolism or drug-drug interaction studies. The clinical programme focused on characterising the pharmacokinetics of memantine following administration of the applicant's prolonged release formulation (absorption kinetics).

The MAA relies in part on the results of clinical trials for the reference product Axura film-coated tablets and in part on new data, relevant for Memantine prolonged release.

Four phase I studies were conducted to characterize the pharmacokinetics and/or bioavailability of memantine FGK capsules. One phase I multiple-dose study of memantine FGK (Study MEM-PK-18), a comparative bioavailability study of various ER formulations of memantine, a food effect and bioequivalence study between the clinical and commercial formulations and a bioavailability study comparing the US commercial IR tablet administered as 10-mg twice daily to the proposed Memantine FGK administered once daily are provided. In addition, a phase I study (MEMPK- 01) demonstrates bioequivalence between the US commercial IR tablets used in the aforementioned bioavailability study and the film-coated tablets used in three of the four main studies underlying the approval of the reference medicinal product Axura.

The results of a population pharmacokinetic (PK) analysis based on data from two phase II trials conducted in patients with diabetic neuropathy (Study MEM-MD-19) or herpetic neuralgia (Study MEM-MD-20) using the United States (US) commercial IR tablet formulation are provided as supportive safety data.

The supportive PK data extracted from one study confirms that there is no bioequivalence between the two formulation types (Memantine FGK versus IR) with respect to the extent of absorption and that the PK parameters of absorption differ significantly (greater exposure) as expected for a higher-dose formulation. Fluctuation is higher for the once-daily administration of the Memantine FGK capsules than for the twice-daily administration of the IR tablet.

These observations justify indubitably the need to investigate the impact of these differences in exposure and peak plasma concentration on efficacy and safety properties by means of phase II and III studies (see below clinical efficacy/safety assessment).

Memantine FGK capsules manufactured in Dublin, Ireland are bioequivalent to the memantine FGK formulation, Inwood, New York with respect to rate and extent of absorption.

There was no significant food effect. The presence of food led to higher inter-subject variability in Cmax compared to administration of the Memantine FGK capsule under fasted conditions and a shorter Tmax but it can be concluded that food has no clinically relevant effect on the bioavailability of memantine MR formulation.

PR dosage forms might be more likely to produce significant adverse effects in case of dose dumping because of the higher doses which are absorbed over a prolonged time. Potential dose dumping effect of ethanol on Memantine FGK capsules should be discussed by the applicant.

The applicant states that there is no difference in the absorption of Memantine FGK prolonged-release capsules when they are taken intact or when the contents are sprinkled on semi-fluid food like applesauce and yoghurt. This affirmation should be supported by bioequivalence data.

Memantine IR has linear pharmacokinetic characteristics over the therapeutic dose range. The applicant is asked to discuss if the plasma exposure of the parent compound increases with dose in a

dose-proportional manner for the Memantine FGK formulation within the range of 7-28mg, in the same way as for the IR formulation.

No study was conducted in the renally and hepatically impaired patients in this submission. However, Memantine FGK being excreted by the kidneys and exhibiting a higher memantine exposure compared to the current IR formulation, the extrapolation of the information summarized in the SmPC to Axura on the drug behaviour in renally impaired patients, the starting dose of the 14mg/day and the up-titration to 28 mg/day in patients with moderate/severe renal impairment should be adequately justified.

Gender and race were not studied in this application.

In the population PK, in the final model, weight was found to be significant ($p < 0.005$) covariate of CL/F, with CL/F increasing with increasing weight (range, 50-129.7 kg). The significance of weight as a covariate of clearance is consistent with other investigations (Findling et al, 2007).

Results in young and elderly healthy adults with memantine treatment support the notion that there are no relevant differences in the effects of memantine FGK with age. On the basis of the described clinical study and in concordance with the Axura SmPC, the recommended dose of memantine FGK for patients >65 years of age is 28 mg per day, i.e. no dose reduction is considered necessary for older patients. However, according to the POPPK results weight- and age-based dosing may be beneficial in patients with neuropathic pain or herpetic neuralgia. The decrease in CL/F with age is probably a reflection of reduced renal function with age. The fact that no dose reduction is judged necessary for the applicant in elderly patients and that the recommended dose of 28 mg per day is maintained in this population should be more discussed and justify in details, in view of the POP PK results.

The use of memantine is not recommended in children. Memantine has not been studied in patients or subjects less than 18 years of age.

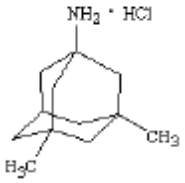
Due to this well established nature, the applicant has not conducted any new drug-drug interaction studies. The information comes from Axura IR formulation.

From a PK perspective, different other concerns should be resolved before approval. Taking into account the absence of bioequivalence versus the IR tablets and the higher exposure for the prolonged release formulation, the results of clinical trials are provided, in addition to the supportive bioavailability/bioequivalence/PK studies.

Pharmacodynamics

Memantine is an orally active N-methyl-D-aspartate receptor antagonist. The chemical name for memantine hydrochloride (HCl) is 1-amino-3,5-dimethyladamantane HCl.

Figure 1.3-1. Chemical Structure of Memantine



The chemical structure of memantine is unrelated to that of acetylcholinesterase inhibitors (AChEIs) and does not affect the inhibition of acetylcholinesterase by donepezil, rivastigmine, or galantamine; nor does the drug bind to muscarinic receptors (Danysz et al, 1997; Enz and Gentsch, 2004; Wenk et al, 2000). These pharmacologic features allow memantine to block the sustained activation of the

receptor hypothesized to occur under pathological conditions such as AD and to rapidly leave the N-methyl-D-aspartate (NMDA) channel during normal physiologic activation of the receptor (Parsons et al, 1999). The pharmacodynamic properties are described correspondingly in the memantine FGK SmPC (Module 1.3.1): 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. Memantine FGK is proposed for the treatment of moderate to severe dementia of the Alzheimer's type with once-daily administration.

Clinical efficacy

Memantine FGK, the drug under application, was developed with the objective of providing a formulation with a slower absorption rate and a higher systemic exposure than those provided by the IR tablet.

The proposed indication for Memantine FGK is "Treatment of patients with moderate to severe Alzheimer's disease."

(As stated earlier),this MAA relies in part on the results of pre-clinical tests and clinical trials for the reference medicinal product Axura film-coated tablets and in part on new data, relevant for memantine FGK.

The clinical development plan for memantine FGK included four bioavailability/pharmacokinetic studies (cf. section 2.1 of this report).

The efficacy of memantine FGK is based on the results of the single pivotal study, MEM-MD-50, which was conducted at 83 study centres in the United States, Argentina, Chile, and Mexico

In addition, three open-label safety studies (MEM-MD-51, MEM-MD-54, and MEM-MD-82) were performed.

Results from seven completed studies using memantine IR at a higher dose (> 20 mg/d) than the currently approved dose for Axura provide additional exposure data.

Specific studies with memantine FGK in patients with renal or hepatic impairment have not been performed. The Applicant states that "although studies with the memantine FGK formulations have not shown any safety risks in patients with renal or hepatic impairment, the memantine FGK SmPC (Module 1.3.1) will follow the dosing suggestions of memantine IR, as presented in the SmPC of the reference medicinal product Axura."

Studies outside the EU were performed in the US, Argentina, Mexico, Chile. A detailed listing is given in Section 1.2.

Dose-response studies and main clinical studies

An earlier dose-finding analysis had indicated increased efficacy with increasing memantine doses from 10 mg to 30 mg, with more pronounced improvement in the Sandoz Clinical Assessment Geriatric Scale (SCAG) with increasing dose (European Public Assessment Report [EPAR] - Initial Scientific Discussion for Approval of Axura.

On the other hand, data from memantine IR studies in non-Alzheimer's disease patients with doses >20 mg suggested a dose-dependent increase in adverse events (AEs), especially at doses of 60 mg/d and 80 mg/d (cf. section 4), in particular with regard to dizziness, and formed the basis for a limitation of the dose increase to at most 30 mg.

Based on this combination of efficacy and safety data, doses above 20 mg, the currently approved maintenance dose, but at most 30 mg, were evaluated for the development of the prolonged-release capsule. An extended time to the maximum plasma concentration (Cmax) with a prolonged-release formulation offered the possibility to increase the dose while potentially reducing the incidence of early onset, concentration-dependent AEs. To increase the daily dose to almost 30 mg and still be able to implement a titration schedule similar to the one used for memantine IR, dose strengths of 7 mg, 14 mg, 21 mg, and 28 mg were chosen. This dosage scheme also provided the possibility to reduce the maintenance dose to 21 mg, if applicable, a dose nearly identical with the established dose of 20 mg for memantine IR.

Memantine FGK was developed to provide a formulation with a slower absorption rate than that of the IR tablet and at a dose that would provide higher systemic exposure than that currently achieved with the 20-mg/d dosing regimen.

The choice of 28 mg once daily for memantine FGK instead of a 20 mg dose once daily memantine IR is not supported by clinical studies and should be further justified **(major objection)**

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table XXX: Summary of efficacy for trial

Title: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients With Moderate to Severe Dementia of the Alzheimer's Type		
Study identifier	**MEM-MD-50**	
Design	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study comparing memantine to placebo in outpatients diagnosed with probable AD (according to DSM-IV-TR and NINCDS-ADRDA criteria) on concurrent donepezil. 1-2 weeks of single-blind placebo treatment followed by 24 weeks of double-blind treatment. Seven clinic visits: Screening, Baseline, and at the end of Weeks 4, 8, 12, 18, and 24. Approximately 600 patients will be enrolled into this study with each of the double-blind treatment groups (memantine or placebo) containing approximately 300 patients. Eligible patients who complete this study may participate in a 28-week open-label study (MEM-MD-54).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 1-2 weeks
Hypothesis	Superiority: The study will be considered "positive" if memantine FGK demonstrated a statistically significant superiority to placebo ($p \leq .05$) on both primary efficacy parameters at Week 24 (LOCF).	
Treatments groups	Memantine FGK/AChEI	Memantine FGK) 7-mg capsules administered orally once a day. The total daily dose was titrated to 28 mg. 1 to 2 weeks of single-blind placebo treatment followed by 24 weeks of double-blind treatment, number randomized: 342

	Placebo/AChEI		<treatment>. <duration>, <number randomized>
Endpoints and definitions	Co-Primary endpoints	Change from Basline in SIB total score CIBIC-Plus Rating score	The primary efficacy parameters in this study are the change from baseline to Week 24 in Severe Impairment Battery (SIB) total score and Clinician's Interview-Based Impression of Change - Plus version (CIBIC-plus) rating score at Week 24.
	Secondary endpoint	Change from baseline in ADCS-ADL19 total score	The secondary efficacy assessment in this study is the 19-Item Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory modified for severity of illness (ADCS-ADL19).
	Additional efficacy endpoints	Change from baseline in the NPI total score. Change from baseline in the verbal fluency test	The Neuropsychiatric Inventory (NPI) is a validated scale that assesses behavioral disturbances with dementia based on responses from the caregiver. There are 12 domain scores and the total score is the sum of the individual domain scores. The verbal fluency test (animal naming) measures impairment in verbal production, semantic memory, and language.
Database lock	The database was locked on January 29, 2008.		

Results and Analysis

Analysis description	**Co-Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) The ITT Population consisted of all patients in the Safety Population (i.e., patients who had a Screening Visit with an assigned screening number, who were randomized into the study, and who received at least one dose of double blind study drug) who completed at least one postbaseline efficacy assessment in SIB or CIBIC-plus. Week 24			
Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI	Memantine FGK/AChEI	<group descriptor>
	Number of subject	327	332	<n>
	Change from baseline in SIB total score			<point estimate>
	Mean	0.3	2.7	
	Median	2.0	2.0	
	Minimum	-76	-30	
	Maximum	29	37	
	LS Mean	-0.4	2.2	
	SD	11.48	11.17	<variability>
	SEM	0.63	0.61	
	SE of LS Mean	0.65	0.65	

Effect estimate per comparison	Change from baseline in SIB total score	Comparison groups	Memantine-Placebo	
		LS Mean Difference	2.6	
		95% Confidence Interval	[1.0, 4.2]	
		P-value	0.001	
Notes	The analyses were performed using using a last-observation-carried-forward (LOCF) approach for the imputation of missing values. The analysis of change from baseline in SIB total score is based on an ANCOVA model with treatment group and study centre as factors, and baseline value as covariate. An MMRM analysis was also performed			
Analysis description	**Co-Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) Week 24			
Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI	Memantine FGK/AChEI	<group descriptor>
	Number of subject	328	333	<n>
	CIBIC-Plus Rating score *Mean* *Median* *Minimum* *Maximum*	 4.1 4.0 1.0 7.0	 3.8 4.0 1.0 7.0	<point estimate>
	SD *SEM*	1.18 0.07	1.22 0.07	<variability>
	CIBIC-Plus Rating score	Comparison groups	Memantine Vs.Placebo	
		Cochran Mantel Haenszel	7.1355	
		P-value	0.008	
Notes	The analyses were performed using using a LOCF approach. The analysis of CIBIC-Plus Rating score is based on a Cochran-Mantel-Haenszel test using modified Ridit scores and controlling for study centre.			
Analysis description	**Secondary analysis** Secondary endpoint			
Analysis population and time point description	Intent to treat (ITT) Week 24			
Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI	Memantine FGK/AChEI	
	Number of subject	328	331	
	Change from baseline in ADCS-ADL19 total score at Week 24 *Mean* *Median* *Minimum* *Maximum* *LS Mean*	 -1.3 0.0 -29 37 -1.7	 -0.7 0.0 -29 20 -1.0	

	SD *SEM* *SE of LS Mean*	7.66 0.42 0.44	6.92 0.38 0.44
Effect estimate per comparison	Change from baseline in ADCS-ADL19 total score at Week 24	Comparison groups	Memantine-Placebo
		LS Mean Difference	0.7
		95% Confidence Interval	[-0.3, 1.8]
		P-value	0.177
Notes	The analysis was performed using a LOCF approach and is based on an ANCOVA model with treatment group and study centre as factors, and baseline value as covariate		
Analysis description	**Secondary analysis** Sensitivity analysis		
Analysis population and time point description	ITT Analysis performed on the observed cases (OC) Week 24		

Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI	Memantine FGK/AChEI	<group descriptor>
	Number of subject	271	270	<n>
	Change from baseline in SIB total score *Mean* *Median* *Minimum* *Maximum* *LS Mean*	 0.5 2.0 -48 29 0.0	 3.2 3.0 -30 37 2.2	<point estimate>
	SD *SEM* *SE of LS Mean*	10.72 0.65 0.67	10.88 0.66 0.69	<variability>

Effect estimate per comparison	Change from baseline in SIB total score	Comparison groups	Memantine-Placebo
		LS Mean Difference	3.0
		95% Confidence Interval	[1.3, 4.6]
		P-value	<0.001
Notes	This is a sensitivity analysis for primary efficacy performed on observed data.		
Analysis description	**Secondary analysis** Sensitivity analysis		
Analysis population and time point description	ITT Analysis performed on the OC Week 24		

Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI	Memantine FGK/AChEI	<group descriptor>
	Number of subject	272	269	<n>

	CIBIC-Plus Rating score *Mean* *Median* *Minimum* *Maximum*		4.1 4.0 1.0 7.0	3.8 4.0 1.0 7.0	<point estimate>
	SD *SEM*		1.18 0.07	1.22 0.07	<variability>
	CIBIC-Plus Rating score	Comparison groups		Memantine Vs.Placebo	
		Cochran Mantel Haenszel		3.8143	
		P-value		0.051	
Notes	This is a sensitivity analysis for primary efficacy performed on observed data.				
Analysis description	**Secondary analysis** Secondary endpoint				
Analysis population and time point description	Intent to treat (ITT) Week 24				
Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI		Memantine FGK/AChEI	
	Number of subject	328		331	
	Change from baseline in ADCS-ADL19 total score at Week 24 *Mean* *Median* *Minimum* *Maximum* *LS Mean*	 -1.3 0.0 -29 37 -1.7		 -0.7 0.0 -29 20 -1.0	
	SD *SEM* *SE of LS Mean*	7.66 0.42 0.44		6.92 0.38 0.44	
Effect estimate per comparison	Change from baseline in ADCS-ADL19 total score at Week 24	Comparison groups		Memantine-Placebo	
		LS Mean Difference		0.7	
		95% Confidence Interval		[-0.3, 1.8]	
		P-value		0.177	
Notes	The analysis was performed using a LOCF approach and is based on an ANCOVA model with treatment group and study centre as factors, and baseline value as covariate				
Analysis description	**Secondary analysis** Additional efficacy parameters				
Analysis population and time point description	Intent to treat (ITT) Week 24				
Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI		Memantine FGK/AChEI	
	Number of subject	321		318	

	Change from baseline in NPI total score at Week 24 *Mean* *Median* *Minimum* *Maximum* *LS Mean*	 -1.6 -1.0 -42 60 -1.3	 -4.3 -2.0 -67 42 -3.9
	SD *SEM* *SE of LS Mean*	12.72 0.71 0.75	14.61 0.82 0.76
Effect estimate per comparison	Change from baseline in NPI total score at Week 24	Comparison groups	Memantine-Placebo
		LS Mean Difference	-2.7
		95% Confidence Interval	[-4.5, -0.8]
		P-value	0.005
Notes	The analysis was performed using a LOCF approach and is based on an ANCOVA model with treatment group and study centre as factors, and baseline value as covariate		
Analysis description	**Secondary analysis** Additional efficacy parameters		
Analysis population and time point description	Intent to treat (ITT) Week 24		
Descriptive statistics and estimate variability	Treatment group	Placebo/AChEI	Memantine FGK/AChEI
	Number of subject	326	330
	Change from baseline in verbal fluency total words count at Week 24 *Mean* *Median* *Minimum* *Maximum* *LS Mean*	 -0.3 0.0 -8 9 -0.7	 0.3 0.0 -9 10 -0.1
	SD *SEM* *SE of LS Mean*	2.47 0.14 0.15	2.79 0.15 0.15
Effect estimate per comparison	Change from baseline in verbal fluency total words count at Week 24	Comparison groups	Memantine-Placebo
		LS Mean Difference	0.5
		95% Confidence Interval	[0.2, 0.9]
		P-value	0.004
Notes	The analysis was performed using a LOCF approach and is based on an ANCOVA model with treatment group and study centre as factors, and baseline value as covariate		

Statistically significant results were obtained for the co-primary endpoints SIB and CIBIC plus using the LOCF approach for imputation of missing data, and confirmed by a sensitivity analysis using the MMRM approach with unstructured correlation matrix (p-value SIB 0.001 and 0.004 respectively, p-value CIBIC-plus 0.008 and 0.003 respectively).

For the secondary efficacy parameter, ADCS ADL19 total score, the difference recorded was not statistically significant (p-value ADCS ADL19 0.177). ADCS ADL19 was evaluated as a secondary parameter. According to the recommendations of guideline CPMP/EWP/553/95 Rev. 1, the co-primary endpoints should preferably reflect the cognitive and the functional domain of impairment.

Clinical studies in special populations

Specific studies with memantine FGK in patients with renal or hepatic impairment have not been performed. The Applicant states that "although studies with the memantine FGK formulations have not shown any safety risks in patients with renal or hepatic impairment, the memantine FGK SmPC (Module 1.3.1) will follow the dosing suggestions of memantine IR, as presented in the SmPC of the reference medicinal product Axura."

A number of ancilliary analyses have been performed:

Subgroup analyses

Sex There was no statistically significant treatment-group–by-sex interaction. Overall, the results support the conclusion that memantine FGK/AChEI treatment is beneficial in both male and female patients.

Age Although there was a suggestion of greater efficacy with memantine FGK/AChEI in younger patients (< 75 years) compared with older patients (≥ 75 years), there was no consistent evidence that the treatment effect depended on age when the effect was examined at individual ages.

Race There was no statistically significant treatment-group-by-race interaction.

Country There was no statistically significant treatment-group–by-country interaction. Overall, the results support the conclusion that memantine FGK/AChEI treatment is beneficial in both US and non-US patients.

Donepezil Intent-to-Treat Population Analysis

Results: At Week 24 (LOCF analysis), the mean CIBIC-plus rating for the memantine FGK/donepezil treatment group was 3.8 compared with a mean in the placebo/donepezil treatment group of 4.0. The mean difference of 0.2 between the two groups was not statistically significant (p = 0.165). At Week 24 (LOCF analysis), the LS mean change from baseline in the ADCS-ADL19 score for the memantine FGK/donepezil treatment group was -1.1 compared with an LS mean change in the placebo/donepezil treatment group of -1.2. The mean difference of 0.1 between the two groups was not statistically significant (p = 0.894).

Analysis performed across trials (pooled analyses AND meta-analysis)

NA

Supportive studies

Studies MEM-MD-54, MEM-MD-82, MEM-MD-51:

Efficacy was not assessed in the safety extension studies MEM-MD-54 and MEM-MD-82 or the long-term safety study MEM-MD-51. However, the low rate of treatment discontinuation in each of the studies provides an indication of prolonged efficacy with memantine FGK treatment. Thus no patient in

the MEM-MD-54 and MEM-MD-51 studies discontinued the study due to insufficient therapeutic response and only one out of 66 patients (1.5%) discontinued study MEM-MD-82 for that reason (Table 10.1-1 in each study report).

Discussion on clinical efficacy

Design and conduct of clinical studies

The duration of the pivotal study MEM MD 50 is only 6 months, whereas rather a duration of 6-12 months is recommended to allow the assessment of a clinically meaningful benefit (CPMP/EWP/553/95).

Ideally, following the recommendations of guideline CPMP/EWP/553/95 Rev. 1, the co-primary endpoints should preferably reflect the cognitive and a functional domain of impairment. In the pivotal study the co-primary endpoints were situated in the global and cognitive domain, whereas the functional domain parameter was evaluated as a secondary parameter.

The external validity of the study is questioned:

-Restrictions of the study population (e.g. exclusion of patients who had evidence of clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease, of patients with a history of alcoholism, of patients taking unapproved medications).

-Baseline data show an imbalance of the number of Caucasians/ non-Caucasians, and Female/Male.

-The Applicant claims that “The population of North- and South American patients with moderate to severe AD in Study MEM-MD-50, as defined by inclusion and exclusion criteria, is comparable to the to-be treated population of patients with moderate to severe AD in Europe.” And “The compound memantine has linear pharmacokinetics, an absolute bioavailability of approximately 100%, low metabolism.

A number of uncertainties exist as regards the concomitant use of ACHEI:

-It is not clear how the differences in concomitant ACHEI medication have been accounted for in the final analysis.

-The pivotal clinical study was conducted with memantine FGK as an add-on treatment. However after amendment 2 this isn’t any longer a requirement. The SPC doesn’t present memantine FGK as an add-on treatment.

-A completed study in healthy volunteers demonstrated an absence of any pharmacokinetic or pharmacodynamic interaction between memantine and donepezil (Periclou et al, 2004). However, interactions with other ACHEI have not been addressed.

Conclusions on clinical efficacy (Efficacy data and additional analyses)

Robust, statistically significant results were obtained for the co-primary endpoints SIB and CIBIC plus using the LOCF approach for imputation of missing data, and confirmed by a sensitivity analysis using the MMRM approach with unstructured correlation matrix (p-value SIB 0.001 and 0.004 respectively, p-value CIBIC-plus 0.008 and 0.003 respectively).

For the secondary efficacy parameter, ADCS ADL19 total score, a functional parameter, which according to the Guideline would need to be upgraded in importance, the difference recorded was not statistically significant (p-value ADCS ADL19 0.177).

It is suggested that the treatment effect does not depend on age. However, the possibility of effect modification by age can not be precluded.

The pattern of missing data, in particular patient withdrawals should be described considering the timing of withdrawal, reasons of withdrawal and consequent imputation for the primary analysis. The influence of the chosen method for handling missing data on the estimated effect should be discussed. Sensitivity analyses are based on a MAR assumption. The validity of this assumption in the context of this particular trial should be discussed considering the CHMP guideline on missing data. It should be discussed whether the resulting estimates are free from important bias. Other sensitivity analyses should be conducted to investigate robustness of efficacy results to methods for handling missing data. Analyses that do not assume MCAR or MAR should be included, considering available CHMP guidance.

Uncertainties exist with respect to both the internal and external validity of a pivotal study.

Clinical safety

For the purpose of the pooled/integrated analysis of safety data, clinical studies with memantine have been organized into three groups (cf. tables below), based on the study population, indications of the studies, and availability of the data for inclusion into an electronic ISS database.

Table 5.1–1. Overview of Group 1 Studies

Study ID (Countries)	*Study Objectives*	*Design*	*Indication*	*Treatment Duration*	*Treatment (Estimated Sample Sizes)*
MEM-MD-50 (Argentina, Chile, Mexico, and US)	Efficacy and Safety	Phase III, double-blind, randomized, parallel, placebo-controlled	Moderate to Severe Alzheimer's Disease (AD)	24 weeks	Placebo (n = 338) Memantine ER (n = 338)
MEM-MD-51 (US)	Safety	Phase III, open-label	Moderate to Severe AD	52 weeks	Memantine ER (n = 166)
MEM-MD-54 (Argentina, Chile, Mexico, and US)	Safety	Phase III, open-label extension to MEM-MD-50	Moderate to Severe AD	28 weeks	Memantine ER (n = 492)
MEM-MD-82	Safety	Phase III, open-label extension to MEM-MD-51 and MEM-MD-54	Moderate to Severe AD	52 weeks	Memantine ER (n = 21)

Table 5.2-1. Overview of Group 2 Studies

Study ID (Countries)	*Study Objectives*	*Design*	*Indication*	*Treatment Duration*	*Treatment (Sample Size)*
MEM-MD-06A	Efficacy and Safety	Phase III, double-blind placebo-controlled	Painful diabetic neuropathy	16 weeks	Placebo (n = 266) Memantine IR 40 mg/d (n = 259)
MEM-MD-06B	Safety	Phase III, open-label extension (to MEM-MD-06A)	Painful diabetic neuropathy	40 weeks	Memantine IR 40 mg/d (n = 393)
MEM-MD-06C	Efficacy and Safety	Phase III, double-blind fixed dose extension (to MEM-MD-06B)	Painful diabetic neuropathy	16 weeks	Memantine IR 40 mg/d (n = 28) Memantine IR 60 mg/d (n = 25) Memantine IR 80 mg/d (n = 26)
MEM-MD-19	Efficacy and Safety	Phase II, double-blind placebo-controlled	Painful diabetic neuropathy	17 weeks	Placebo (n = 52) Memantine IR 60 mg/d (n = 51)
MEM-MD-20	Efficacy and Safety	Phase II, double-blind placebo-controlled	Postherpetic neuralgia	17 weeks	Placebo (n = 46) Memantine IR 60 mg/d (n = 51)
MEM-MD-27	Efficacy, safety and tolerability	Phase II, open label, pilot efficacy, safety, and tolerability	Bipolar I acute mania	3 weeks	Memantine IR 20 - 30 mg/d (n = 12) Memantine IR 20 - 40 mg/d (n = 12) Memantine IR 20 - 50 mg/d (n = 11)

Adverse events

In the Group 1A placebo-controlled Study MEM-MD-50, the incidence of TEAEs was similar between the patients receiving memantine FGK and those receiving placebo (62.5% and 61.8%, respectively). The profile of TEAEs was also similar between the two treatment groups. Among memantine FGK patients, the TEAEs reported at an incidence of at least 5% were fall (5.6%), headache (5.6%), urinary tract infection (5.3%), and diarrhoea (5.0%). Among the placebo patients, the most frequently reported TEAEs were fall (7.8%), urinary tract infection (6.9%), and headache (5.1%). Most of the TEAEs were reported during the first 3 months of treatment. The only TEAE reported in at least 5% of memantine

FGK patients, and at an incidence of at least twice that of placebo patients, was dizziness (4.7% vs. 1.5%). None of the cases of dizziness resulted in a fall. Most TEAEs were considered mild or moderate in severity and not related to the study drug.

Table 2.1-2. Most Frequently Reported ADRs (≥ 1% of patients with possibly related and all [≥ 1 patient] with related TEAEs in Either Treatment Group) Among Patients in the Placebo-Controlled Memantine ER Clinical Study MEM-MD-50—Safety Population

	Placebo (N = 335)		*Memantine ER (N = 341)*	
	n (%)		*n (%)*	
	Possibly related	*Related*	*Possibly related*	*Related*
Patients with at least one TEAE	**55 (16.4)**	**2 (0.6)**	**82 (24.0)**	**7 (2.1)**
Dizziness	4 (1.2)	0	9 (2.6)	2 (0.6)
Headache	3 (0.9)	0	7 (2.1)	1 (0.3)
Agitation	5 (1.5)	0	6 (1.8)	0
Insomnia	3 (0.9)	1 (0.3)	6 (1.8)	0
Somnolence	3 (0.9)	0	6 (1.8)	0
Weight increased	2 (0.6)	0	5 (1.5)	0
Depression	1 (0.3)	0	5 (1.5)	0
Fall	4 (1.2)	0	5 (1.5)	0
Hypertension	4 (1.2)	0	5 (1.5)	0
Asthenia	1 (0.3)	0	4 (1.2)	0
Constipation	2 (0.6)	0	4 (1.2)	0
Confusional state	4 (1.2)	0	3 (0.9)	0
Diarrhoea	4 (1.2)	0	3 (0.9)	0
Sedation	0	0	3 (0.9)	1 (0.3)
Delirium	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Irritability	4 (1.2)	1 (0.3)	2 (0.6)	0
Weight decreased	4 (1.2)	0	3 (0.9)	0
Head injury	0	0	0	1 (0.3)
Psychotic disorder	0	0	0	1 (0.3)
Pruritus	0	0	0	1 (0.3)
Rash	2 (0.6)	0	0	1 (0.3)

ER = extended release; TEAE = treatment-emergent adverse event. Cross-reference: Table 14.5.1.5 in MEM-MD-50

In the Group 1B open-label Studies MEM-MD-51 and MEM-MD-54, 450 (68.7%) patients receiving memantine FGK reported at least one TEAE. The most commonly reported TEAEs (≥ 5%) were fall (7.8%), urinary tract infection (7.6%), dizziness (5.3%), and agitation (5.0%). The profile of the TEAEs was similar to the TEAEs reported in the placebo-controlled Study MEM-MD-50. Among the 214 patients who were treated with memantine FGK for at least 1 year, 168 (78.5%) experienced at least one TEAE. The most frequently reported TEAEs were fall (8.9%); urinary tract infection (7.5%); diarrhoea (7.0%); dizziness, headache, cough, and weight decreased (6.5% each); agitation, weight increased, and influenza (6.1% each); and confusional state, depression, and hypertension (5.1% each). Patients prolonging memantine FGK treatment in the long-term safety extension Study MEM-

MD-82 (Group 1S) most frequently reported urinary tract infection as TEAE (13.6% of patients), followed by agitation (12.1%) and aggression (10.6%). 96.1% of the TEAEs were considered unrelated to study medication treatment by the investigator.

In the Group 2 placebo-controlled studies in non-AD patients (MEM-MD-06A, MEM-MD- 19, and MEM-MD-20), 272 (75.3%) patients receiving memantine IR and 272 (74.7%) patients receiving placebo experienced at least one TEAE. TEAEs reported in at least 5% of memantine IR patients, and at an incidence at least twice that of placebo patients, across the three studies were dizziness (23.8% vs. 3.8%) and fatigue (8.6% vs. 3.8%). The dosages of memantine IR used in these studies were as high as 60 mg/d. In the Group 2 non–placebo controlled extension Studies MEM-MD-06B and MEM-MD-06C, dizziness was the most frequently reported TEAE, **with the incidence of dizziness being dose related**; in Study MEMMD- 06C, 30.8% of patients treated with memantine IR at 80 mg/d experienced dizziness compared with 12.0% of patients treated with 60 mg/d and 7.1% of patients treated with 40 mg/d.

Across the Group 3 clinical pharmacology studies, the most frequently reported TEAEs (≥ 5%) among subjects taking memantine (ER and/or IR) were headache (31.6%), dizziness (27.6%), somnolence (11.2%), nausea (7.1%), back pain (6.1%), and vomiting (5.1%).

The pattern of the most frequently reported adverse reactions with memantine FGK is similar to that known for the reference product Axura.

The adverse reactions, based on the analysis of the safety data from study MEM-MD-50, differ in some aspects from those observed with the reference product. E.g. it should be noted that both syncope and bradycardia, are mentioned as uncommon adverse events.

Serious adverse events and deaths

In the Group 1A placebo-controlled Study MEM-MD-50, 4 patients (1.2% or 2.9 per 100 patient-years) treated with memantine FGK died due to fatal SAEs that occurred during the study or within 30 days of the last dose of memantine FGK compared with five patients (1.5%, or 3.5 per 100 patient-years) treated with placebo. All of the deaths in the memantine patients were judged by the Investigator to be not related to treatment. An additional 30 (4.6%) patients died in the open-label.

Group 1B studies and three (4.5%) patients died in the Group 1S long-term extension Study MEM-MD-82. Causes of death were primarily attributed to cardiovascular and cerebrovascular events and pneumonia and were consistent with the background of concurrent medical illnesses observed in this population of elderly patients with moderate to severe AD.

An additional four (0.7%) memantine-treated patients died in the Group 2 studies (all in Study MEM-MD-06B) compared with one (0.3%) placebo-treated patient (in Study MEM-MD-06A).

In the Group 1A placebo-controlled Study MEM-MD-50, SAEs (including the deaths described above) were reported in 28 (8.2%) patients treated with memantine FGK compared with 21 (6.3%) patients treated with placebo. There were no SAEs reported at an incidence of 1% or higher in memantine FGK patients. In the open-label.

Group 1B studies, 97 (14.8%) patients experienced at least one SAE during treatment periods of up to 1 year; the most frequently reported SAEs were fall (2.9%), pneumonia (2.3%), and hip fracture (1.1%). A total of 17 (25.8%) patients experienced SAEs in Study MEM-MD-82 (Group 1S), most frequently dementia Alzheimer's type (3 patients), aggression (2 patients), pneumonia (2 patients), and respiratory failure (2 patients). Most of the SAEs were considered to be not or unlikely related to the study drug. The SAEs reported appeared more likely to be related to the underlying illness of the patients rather than the use of the study drug.

In the placebo-controlled Group 2 studies in non-AD patients, 23 (6.4%) patients receiving memantine IR and 16 (4.4%) patients receiving placebo experienced at least one SAE. In the non–placebo-controlled Group 2 studies in non-AD patients, 54 (10.7%) patients receiving memantine IR experienced at least one SAE. Most of the SAEs were judged to be not related to study drug. None of the 98 healthy volunteers who received memantine FGK in the Group 3 studies experienced an SAE.

Laboratory findings

Analysis of vital signs measurements, clinical laboratory data, and ECG results in the Group 1 studies (double-blind and open-label) in AD patients did not raise any safety concerns. The incidence of PCS values was generally low, and mean changes from baseline in vital sign, ECG, and clinical laboratory parameters in patients receiving memantine FGK were small in magnitude and similar to those observed in patients receiving placebo.

Table 4.2-2. Number and Percentage of Patients with Potentially Clinically Significant Electrocardiographic Parameters in the Placebo-Controlled Memantine ER Clinical Study MEM-MD-50—Safety Population

Parameter	*PCS Criterion*	*Placebo (N = 335)*	*Memantine ER (N = 341)*
		n/N1 (%)	*n/N1 (%)*
PR interval, msec	≥ 250	0/283	0/295
QRS interval, msec	≥ 150	1/297 (0.3)	1/308 (0.3)
QTc Bazett, msec	> 500	2/301 (0.7)	1/309 (0.3)
QTc Fridericia, msec	> 500	0/301	2/309 (0.6)

ER = extended release; N = number of patients in treatment group; N_1 = number of patients with a non-PCS baseline value and at least one postbaseline value during double-blind treatment; n = subgroup of N_1 with at least one PCS postbaseline value during double-blind treatment; PCS = potentially clinically significant.

Cross-reference: After-Text Table 11.3.1.

Table 4.2-5. Number and Percentage of Patients with Potentially Clinically Significant Electrocardiographic Parameters in the Open-Label Memantine ER Clinical Studies MEM-MD-54 and MEM-MD-51—Safety Population

Parameter	*PCS Criterion*	*MEM-MD-54*		*MEM-MD-51*	*All Patients*
		Plc/Mem (N = 245)	*Mem/Mem (N = 246)*	*Mem (N = 164)*	*(N = 655)*
		n/N1 (%)	**n/N1 (%)**	**n/N1 (%)**	**n/N1 (%)**
PR interval. msec	≥ 250	1/211 (0.5)	0/213	1/128 (0.8)	2/552 (0.4)
QRS Interval msec	≥ 150	3/220 (1.4)	2/220 (0.9)	4/134 (3.0)	9/574 (1.6)
QTc Bazett, msec	> 500	4/223 (1.8)	2/221 (0.9)	1/139 (0.7)	7/583 (1.2)
QTc Fridericia, msec	> 500	2/223 (0.9)	1/221 (0.5)	2/139 (1.4)	5/583 (0.9)

Studies MEM-MD-51 and MEM-MD-54

ER = extended release; Mem = memantine; N = number of patients in treatment group; N_1 = number of patients with a non-PCS baseline value and at least one postbaseline value during open-label treatment; n = subgroup of N_1 with at least one PCS postbaseline value during open -label treatment; Plc = placebo; PCS = potentially clinically significant.

Cross-reference: After-Text Table 11.3.2.

The only clinical laboratory, vital sign, or ECG parameters that were recorded as PCS in at least 3% of memantine FGK patients in Study MEM-MD-50 were BUN increased (3.1% vs. 3.2% in placebo patients), weight increased (9.8% vs. 8.2% in placebo patients), and weight decreased (3.9% vs. 5.4% in placebo patients).

Similar results were generally obtained in the Group 2 memantine IR studies using dosages greater than 20 mg/d. However, in Studies MEM-MD-06B and MEM-MD-06C, which were conducted in patients with diabetes, small increases in creatinine and BUN were observed at end of study, and the incidences of PCS values for BUN and urine glucose were relatively high; these changes were to be expected in a population of patients with diabetes. In these two studies all patients received memantine at dosages from 40 to 80 mg/d.

Table 4.2-9. Number and Percentage of Patients with Potentially Clinically Significant Electrocardiographic Parameters in the Non–Placebo-Controlled Memantine IR Clinical Studies—Safety Population

Parameter	*PCS Criterion*	*MEM-MD-06B*		*MEM-MD-06C*	*MEM-MD-27*
		Plc/Mem (N = 210)	*Mem/Mem (N = 183)*	*Mem (N = 79)*	*Mem (N = 35)*
		n/N1 (%)	**n/N1 (%)**	**n/N1 (%)**	**n/N1 (%)**
PR interval, msec	≥ 250	0/178	3/161 (1.9)	0/68	0/24
QRS Interval, msec	≥ 150	1/180 (0.6)	4/162 (2.5)	1/68 (1.5)	0/24
QTc Bazett, msec	≥ 500	5/179 (2.8)	2/161 (1.2)	0/71[a]	1/25 (4.0)
QTc Fridericia, msec	≥ 500	—	—	—	0/25

a QT interval uncorrected in Study MEM-MD-06C.

IR = immediate release; Mem = memantine; N = number of patients in treatment group; N_1 = number of patients with a non-PCS baseline value and at least one postbaseline value during the study; n = subgroup of N_1 with at least one PCS postbaseline value during the study; Plc = placebo; PCS = potentially clinically significant.

Cross-reference: Study MEM-MD-06B, Table 14.5.6.1A; Study MEM-MD-06C, Table 14.5.6.1A; Study MEM-MD-27, Table 14.5.6.1.

In Study MEM-MD- 19, which was also conducted in a population of diabetic patients, the incidence of PCS elevations in urinary glucose was twice as high in the memantine IR patients as in placebo patients (27.0% vs. 11.8%).

In the Group 3 memantine FGK clinical pharmacology studies, no clinically important trends were noted in vital signs or clinical laboratory data. No ECG result met the criteria for potential clinical significance.

It should be noted however that in a small number of patients in studies MEM MD 50, 51 and 54 (Group 1, memantine FGK) and in studies MEM MD 06B and MEM MD 27 (Group 2, memantine IR), a prolonged QT interval > 500 msec has been recorded.

A summary of cardiovascular safety:QT/QTc Intervals and other relevant clinical and nonclinical data (September 21, 2006) is included in appendices 9.2 and 9.3 of the clinical summary.

"The Applicant has conducted a study to investigate the risk of QT prolongation in patients treated with memantine. In this study, supratherapeutic doses of memantine (till 80 mg/day) were assessed. Very few cases with significant QT prolongation were reported, according to the ICH guideline criteria (E14). In all cases (including the fatal cases), major confounding factors were present (concomitant use of other QT prolonging-drugs, elderly patients, patients with preexisting cardiac disease or hypokalemia…). Very few cases of QT prolongation longer than 500 msec were reported). No episode of torsades de pointes was documented in the study.

Safety in special populations

The TEAE profile in Study MEM-MD-50 did not appear to vary significantly when analysed based on sex, age, or race.

Whereas a possible influence of age cannot be precluded with regard to efficacy, from a safety point of view the TEA profile in study MEM MD 50 did not vary significantly based on age. However, the POPPK data (see section 2.1.9) probably reflect a reduced renal function with age.

It should be noted that the safety profile in the specific populations of patients suffering from renal insufficiency or hepatic insufficiency has not been investigated.

Immunological events

NA

Safety related to drug-drug interactions and other interactions

Analysis of TEAEs did not reveal any evidence of an interaction of memantine with AChEIs, antihypertension medications, sedatives, antidepressants, antipsychotic medications, or acetylsalicylic acid and NSAIDs. The demographic profile of patients based on AChEI used is presented in After-Text Table 3.1.1E of the SCS; there were no meaningful differences in demographic profile between treatment groups based on AChEI use.

There was no evidence of a potential drug-disease interaction with memantine FGK based on an analysis of TEAEs. Only hypertension was formally analysed, since it was the only preferred term included in the medical history of at least 25% of patients; the numbers of patients with medical histories of other diseases (by preferred term) were too small to allow meaningful comparisons.

There were no apparent differences in the TEAE incidence or profile based on hypertension status, and no apparent effects of memantine based on hypertension status.

No new drug-drug interaction studies have been performed. A detailed description of interactions of the reference medicinal product Axura is presented in the SPC. This information also applies to memantine FGK.

Discontinuation due to AES

In the Group 1A placebo-controlled Study MEM-MD-50, discontinuations associated withAEs were reported in 34 (10.0%) patients treated with memantine FGK and 21 (6.3%) patients treated with placebo. Eighty AEs were reported as the cause of premature discontinuation among the 55 patients. The most frequent of these events in the placebo group were congestive cardiac failure and urinary tract infection, which occurred in two patients each. In the memantine FGK group, the most frequent of these events were dizziness (5 patients); agitation (3 patients); and pneumonia, CVA, and depression (2 patients each). The patients who discontinued because of agitation and depression were all from the US. The incidence of discontinuations among non-US patients in both placebo and memantine treatment groups was lower than that of their US counterparts. There was no apparent effect of treatment on the AE leading to discontinuation profile based on age, sex, or race. Overall, the types and incidences of AEs leading to discontinuation were similar between the treatment groups.

In the Group 1B open-label studies, 84 (12.8%) patients treated with memantine FGK discontinued because of an AE. Agitation and dizziness were the most common reasons for discontinuation (1.1%, 7 patients each). A total of eight (12.1%) patients discontinued from the long-term extension Study MEM-MD-82 because of AEs. The AEs most commonly associated with premature discontinuations were dementia Alzheimer's type (3 patients) and respiratory failure (2 patients).

In the Group 2 placebo-controlled studies in non-AD patients, 56 (15.5%) patients receiving memantine IR and 21 (5.8%) patients receiving placebo discontinued as a result of an AE. In these

studies, the dosage of memantine IR was as high as 60 mg/d, which is three times the approved dosage of 20 mg/d. Dizziness was the most frequently reported AE that led to premature discontinuation (3.9%). In the Group 2 open-label studies, 47 (9.3%) patients receiving memantine IR discontinued because of an AE, the most frequently reported of which was dizziness (2.0%).

In the Group 3 clinical pharmacology studies, only one subject discontinued because of an AE (somnolence).

CHMP comment

In the Group 1 placebo-controlled Study MEM-MD-50, discontinuations associated with AEs were reported in 34 (10.0%) memantine FGK- and 21 (6.3%) placebo-treated patients. A total of 80 AEs were reported as the cause of premature discontinuation among the 55 patients. The most frequent of these events in the placebo group were congestive cardiac failure and urinary tract infection, which occurred in two patients each.

In the memantine FGK group, the most frequent of these events were dizziness (5 patients); agitation (3 patients); and pneumonia, cerebrovascular accident, and depression (2 patients each).

A more detailed description and discussion of the AEs resulting in discontinuation of treatment, including severity and relationship to study drug, is requested.

Please provide the CRF's.

Discussion on clinical safety

The pattern of the most frequently reported adverse reactions with memantine FGK is similar to that known for the reference product Axura.

The adverse reactions, based on the analysis of the safety data from study MEM-MD-50, differ in some aspects from those observed with the reference product. E.g. it should be noted that both syncope and bradycardia, are mentioned as uncommon adverse events.

Percentages of deaths were recorded in open label studies as follows: 30 (4.6%) patients died in the open-label Group 1B studies and three (4.5%) patients died in the Group 1S long-term extension Study MEM-MD-82.

No placebo-controlled long term (>24 weeks) safety trials were performed with memantine FGK.

In a small number of patients in studies MEM MD 50, 51 and 54 (Group 1, memantine FGK) and in studies MEM MD 06B and MEM MD 27 (Group 2, memantine IR), a prolonged QT interval > 500 msec has been recorded.

The TEAE profile in Study MEM-MD-50 did not appear to vary significantly when analysed based on sex, age, or race.

Missing information is the safety profile in the specific populations of patients suffering from renal insufficiency or hepatic insufficiency.

There may be a risk for off-label use.

Conclusions on clinical safety

The pattern of the most frequently reported adverse reactions with memantine FGK is similar to that known for the reference product Axura.

The adverse reactions, based on the analysis of the safety data from study MEM-MD-50, differ in some aspects from those observed with the reference product. E.g. it should be noted that both syncope and bradycardia, are mentioned as uncommon adverse events.

Important information with regard to special populations of memantine FGK is missing.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Risk management plan

The applicant states that no important identified risks, important potential risks, or important missing information beyond those already known from the reference medicinal product Axura were determined for Memantine FGK.

For the full safety profile of memantine in addition to the safety data generated in clinical studies with Memantine FGK, full reference is made to the safety information provided in the Axura SmPC.

CHMP comments: The applicant's conclusions are not fully endorsed.

1) General remark: the RMP for Memantine FGK requires full revision and should be based on the RMP for the reference product Axura as a stand-alone document. Cross-references to the Axura RMP are inadequate and all relevant information regarding safety concerns, pharmacovigilance and risk minimisation activities described for the reference product RMP have to be included in the RMP for Memantine FGK. The overview tables in section 1.10, 2, 3 and 5 have to be provided and populated according to the reference product and the remarks listed below.

2) Missing information for Memantine FGK has been identified in the RMP. The applicant is requested to list the following missing information in the appropriate section of the RMP:

- E*ffects of memantine on foetal growth*

Moreover, the applicant is requested to discuss how this missing information could be generated post-authorisation.

4. ORPHAN MEDICINAL PRODUCTS

N/A

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

The difference in absorption kinetics and differences in the plasma concentrations-time profiles observed for the PR formulation in comparison with the IR formulation might affect the efficacy and justify the need to investigate in details the impact of these differences on efficacy properties. These issues are addressed by new efficacy data rather than by new PK data.

In the pivotal study MEM MD 50 (duration 24 weeks), a significant difference in efficacy in favour of memantine FGK compared to placebo was shown.

Uncertainty in the knowledge about the beneficial effects

According to the note for guidance on modified release oral and transdermal dosage forms: section II, for applications for a modified release formulation of a drug that is authorised as an immediate release formulation, paragraph 4.2.1, therapeutic studies are necessary in the majority of cases when the existence of equivalent levels of effect to those obtained with the immediate release cannot be assumed on the basis of the pharmacokinetic data.

Memantine IR for once daily treatment of patients with moderate to severe Alzheimer's disease is available on the market.

The clinical study MEM MD 50, is a placebo-controlled study, though a statistically significant difference was seen on the primary endpoint, the difference was small, whereas the effect on ADL was not statistically significant. Therefore the clinical relevance of the effects are doubtful and may not outweigh the risk. The company should justify the benefit/risk is positive even the more so as a comparison with the immediate release form is lacking.

A clearcut comparison of efficacy and safety of once daily memantine FGK with the memantine IR 20 mg dose on the market is not possible at present. The choice of a dosis of 28 mg once daily should be better justified. (major objection):

The objective of the Applicant is to provide a formulation with a slower absorption rate and a higher systemic exposure than the IR tablet.

The Applicant refers to an analysis with memantine IR showing a dose response across the range of 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, and with a dose-dependent increase in the number of AEs. (The use of this scale is not recommended in patients with Alzheimer's disease)

A limitation of the dose increase to at most 30 mg is based on memantine IR studies with doses > 20 mg which suggested a dose-dependent increase in adverse events especially at doses of 60mg/d and 80 mg/d.

The Applicant suggests that the incidence of dizziness with memantine FGK at the intended in study MEM MD 50 was relatively low compared with the incidence of dizziness in the non-controlled extension studies MEM MD 06B en MEM MD 06C in non-Alzheimer patients treated with memantine IR at doses of 40 to 80 mg/d.

The Applicant suggests that an extended time to the maximum plasma concentration with a prolonged release formulation offers the possibility to increase the dose while potentially reducing the incidence of early onset, concentration-dependent AEs.

It is considered that in the absence of any controlled comparative clinical trial, comparing efficacy and safety, any claim on superiority / non-inferiority in terms of efficacy or safety compared with the treatments already existing on the market, can't be made.

Although the efficacy results in the pivotal study show a statistical significant effect on cognition and global assessment, this was not seen for ADL functioning. Overall the clinical relevance of the effect remains unclear. Additionally the number of subjects in the clinical trial is relatively small so uncertainties remain regarding the safety of a higher AUC. Discussion on the B/R is further hampered by the lack of a direct comparison to memantine IR making it impossible to place the B/R of the current product in to perspective. It should have been envisaged and valuable to perform a head-to-head study comparing efficacy and safety of the IR and the ER forms in patients with Alzheimer's disease including the comparison of the PK profile of the ER formulation with the IR formulation administered 20 mg once daily.

Other shortcomings of the pivotal trial MEMMD50 are:

- one of the primary efficacy parameters was not situated in the functional domain as is recommended in the guideline CPMP/EWP/553/95 Rev 1. The ACDS ADL19 total score was assessed as a secondary parameter and was not significantly different in favour of memantine FGK.
- A well designed study addressing the switch between the IR and memantine FGK formulation would have been needed to draw valid conclusions with regard to this aspect.

Risks

Unfavourable effects

Because of a higher Cmax and a higher fluctuation index for the once daily ER formulation compared to the IR formulation, the sponsor has to demonstrate with clinical studies that this does not lead to a higher incidence/intensity of the adverse events. The claim that the tolerability profile observed for the IR formulation is not compromised when administering the ER formulation 28 mg once daily should be proved by safety data.

Although the safety profile was in line with that known for the IR formulation, adverse effects however differ in some aspects from those observed with the reference product.

In this regard it was noted for example that both syncope and bradycardia, which possibly might be associated with QT-prolongation are mentioned as uncommon adverse events.

Patients who are possibly at risk for adverse effects were excluded from the study population.

As mentioned by NL, the number of subjects in the clinical trials is relatively small and some uncertainties remain regarding the safety off a higher AUC.

Memantine being a well-known and well-characterised active substance, the applicant has not conducted any new drug-drug interaction studies. The information in the dossier comes from Axura IR formulation and literature.

Uncertainty in the knowledge about the unfavourable effects

Important information with regard to special populations of memantine FGK 28mg/day is missing.

No studies of Memantine FGK in specific populations (renal insufficiency, hepatic insufficiency) have been performed.

Inclusion criteria were very narrow. Patients who are most at risk for adverse effects were excluded from the study population. Also non-caucasians and male patients were underrepresented.

No placebo-controlled long term studies have been performed with the memantine FGK formulation.

Literature data show that the risk of off-label use exists.

Balance

According to the Note for guidance on modified release oral and transdermal dosage forms: section II (PK and clinical evaluation), within the context of an application for a modified release formulation of a drug that is authorized as an immediate release formulation, if the drug substance exhibits linear pharmacokinetic properties, it is necessary to compare total exposure between the MR formulation and the IR formulation at one dose level following multiple dose administration.

The aim of the modified release formulation is in general to obtain a similar total exposure as for the IR formulation. Furthermore, the interest of a prolonged release formulation is in general to produce the desirable clinical effect with a lower dose and reduced fluctuations in drug plasma concentrations, avoiding high peak concentrations and reducing the intensity of adverse events. Another advantage is patient convenience which leads to better compliance, by taking the medication once daily for example.

However, in the case of memantine, the immediate release formulation can already be administered as a once daily 20 mg dose. Secondly, the supportive PK data extracted from the study MEM-Pk-23 confirms that there is no bioequivalence between the two formulation types with respect to the extent of absorption and that the PK parameters of absorption differ significantly (greater exposure) as expected for a higher-dose formulation. Thirdly, fluctuation is higher for the once-daily administration of the ER capsules than for the twice-daily administration of the IR tablet.

These observations justified indubitably the need to investigate the impact of these differences in exposure and peak plasma concentration on efficacy and safety properties by means of phase II and III studies.

In the context of a hybrid application, for which the marketed IR formulation Axura film-coated tablets serves as the reference product, a head-to-head trial should have been performed in patients with moderate to severe Alzheimer's disease to compare efficacy and safety of the 28 mg ER formulation versus memantine IR 20 mg.

A formal dose finding study justifying the selection intended dose is lacking in the application dossier.

In the absence of any controlled comparative clinical trial, comparing efficacy and safety, any claim on superiority / non-inferiority compared with the treatments already existing on the market, can't be made.

In the pivotal study MEM MD 50 (duration 24 weeks), a significant difference in efficacy in favour of memantine FGK compared to placebo on a background of an ACHEI, was shown.

5.1. Conclusions

The overall B/R ratio of memantine FGK is negative for the dosages exceeding 20 mg/day.

6. RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

6.1. Conditions for the marketing authorisation

None

6.2. Summary of product characteristics (SmPC)

The latest update of the originator's SmPC has not been implemented in the generic SmPC yet. To harmonize the generic SmPC with the originator's SmPC, (i.e., inclusion of the following adverse reactions in section 4.8: Balance disorders, Elevated liver function test, Hepatitis) please refer to the current originator's SmPC (EMEA/H/C/000463-IB/0074/G; last updated 12/06/2012).

For comments, see annexed document

6.3. Labelling

None

6.4. Package leaflet (PL)

With regard to the comment on the generic product's SmPC, the Marketing Authorisation Applicant is asked to harmonise the PL accordingly

User consultation

The bridging report will be provided at D121.