Public Assessment Report

Decentralised Procedure

YMANA 5, 10, 15 and 20 mg Film-coated Tablets

(memantine hydrochloride)

Procedure No: UK/H/5384/001-04/DC

UK Licence No: PL 34088/0034-0037

ALKALOID-INT d.o.o.,
This is a summary of the public assessment report (PAR) for YMANA 5, 10, 15 and 20 mg Film-coated Tablets (memantine hydrochloride). It explains how YMANA 5, 10, 15 and 20 mg Film-coated Tablets were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use YMANA 5, 10, 15 and 20 mg Film-coated Tablets.

For practical information about using YMANA 5, 10, 15 and 20 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are YMANA 5, 10, 15 and 20 mg Film-coated Tablets and what are they used for?**

YMANA 5, 10, 15 and 20 mg Film-coated Tablets are medicines that contain the active substance memantine (as hydrochloride). They are used for the treatment of patients with moderate to severe Alzheimer’s disease, a type of dementia (a brain disorder) that gradually affects memory, intellectual ability and behaviour.

YMANA 5, 10, 15 and 20 mg Film-coated Tablets are generic medicines. This means that YMANA 5, 10, 15 and 20 mg Film-coated Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Ebixa 5,10, 15 and 20 mg Film-coated Tablets (H. Lundbeck A/S).

**How are YMANA 5, 10, 15 and 20 mg Film-coated Tablets used?**

YMANA 5, 10, 15 and 20 mg Film-coated Tablets are taken by mouth. The whole tablet should be swallowed with some water and can be taken with or without food. The 10 mg and 20 mg tablet can be divided into equal doses.

The recommended dose of Ymana tablets for adults and elderly patients is 20 mg once a day. The usual starting dose is 5 mg a day for the first week. This is increased to 10 mg a day in the second week and to 15 mg a day in the third week. From the fourth week onwards, the usual dose is 20 mg once a day.

YMANA 5, 10, 15 and 20 mg Film-coated Tablets can only be obtained on prescription from a doctor.

For further information on how YMANA 5, 10, 15 and 20 mg Film-coated Tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

**How do YMANA 5, 10, 15 and 20 mg Film-coated Tablets work?**

The active substance in YMANA Tablets, memantine, is an antideementia medicine. Memory loss in Alzheimer’s disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory. Memantine belong to a group of medicines called (NMDA) receptor antagonists. Memantine acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

**How have YMANA 5, 10, 15 and 20 mg Film-coated Tablets been studied?**

YMANA 5, 10, 15 and 20 mg Film-coated Tablets are generic medicines. Memantine hydrochloride was designated a BCS Class I drug based on its properties (highly soluble, highly permeable). With this application the applicant claimed BCS biowaiver.

**What are the benefits and risks of YMANA 5, 10, 15 and 20 mg Film-coated Tablets?**

As YMANA 5, 10, 15 and 20 mg Film-coated Tablets are generic medicines of the reference medicine, Ebixa 5, 10, 15 and 20 mg Film-coated Tablets (H. Lundbeck A/S), their benefits and risks are taken as being the same as those for Ebixa 5, 10, 15 and 20 mg Film-coated Tablets (H. Lundbeck A/S).
Why are YMANA 5, 10, 15 and 20 mg Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, YMANA 5, 10, 15 and 20 mg Film-coated Tablets have been shown to have comparable quality and bioequivalent to Ebixa 5, 10, 15 and 20 mg Film-coated Tablets. Therefore, the view was that, as for Ebixa 5, 10, 15 and 20 mg Film-coated Tablets, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of YMANA 5, 10, 15 and 20 mg Film-coated Tablets?
A risk management plan has been developed to ensure that YMANA 5, 10, 15 and 20 mg Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for YMANA 5, 10, 15 and 20 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about YMANA 5, 10, 15 and 20 mg Film-coated Tablets
Bulgaria, Croatia, Slovenia and the UK agreed to grant Marketing Authorisations for YMANA 5, 10, 15 and 20 mg Film-coated Tablets on 15th September 2014. Marketing Authorisations were granted in the UK on 7th October 2014.

The full PAR for YMANA 5, 10, 15 and 20 mg Film-coated Tablets follows this summary. For more information about treatment with YMANA 5, 10, 15 and 20 mg Film-coated Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in December 2014.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the applications for YMANA 5, 10, 15 and 20 mg Film-coated Tablets for the treatment of patients with moderate to severe Alzheimer’s disease is approvable.

The applications were submitted using the Decentralised Procedure (DCP) with the UK as the RMS and Bulgaria, Croatia and Slovenia as CMSs. The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended and cross referred to Ebixa 5, 10, 15 and 20 mg Film-coated tablets, which were first licensed to H. Lundbeck A/S (EU/1/02/219) on 15th May 2002 via the centralised procedure.

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.

Since memantine hydrochloride is a BCS Class I drug, the applicant has claimed BCS biowaiver. A bioequivalence study with the 20 mg strength was also submitted, as supporting data.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

All involved Member States agreed to grant Marketing Authorisations for the above products at the end of the procedure (Day 210 – 15th September 2014). After a subsequent national phase, the UK granted Marketing Authorisations (PL 34088/0034-0037) for these products on 7th October 2014.

II QUALITY ASPECTS

II.1 Introduction
These products are film-coated tablets and contain 5, 10, 15 and 20 mg memantine hydrochloride, as active ingredient, which are equivalent to 4.15, 8.31, 12.46 and 16.62 mg memantine respectively. The excipients present are silicified microcrystalline cellulose, croscarmellose sodium, talc, magnesium stearate making up the tablet core and the film-coating consisting of hypromellose, Macrogol 400, titanium dioxide (E171), yellow iron oxide (E172) (15 mg) and red iron oxide (E172) (20 mg).

The excipients croscarmellose sodium, talc and magnesium stearate comply with their respective European Pharmacopoeia monographs. Silicified microcrystalline cellulose and film-coating materials comply with satisfactory in-house specifications.

None of the excipients are sourced from animal or human origin. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

For 5 mg and 15 mg:
The finished product is packaged in aluminium/polyvinylchloride (PVC) blister packs containing 7 tablets per blister strip. Pack size of 7 tablets are authorised.

For 10 mg and 20 mg:
The finished product is packaged in aluminium/polyvinylchloride (PVC) blister packs containing either 7, 10 or 14 tablets per blister strip. Pack sizes of 7, 28 and 30 tablets are authorised.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: Memantine hydrochloride
Chemical name(s): 1-амино-3,5-диметилтрисцикло [3.3.1.1 (3.7)]-декан гидрохлорид
Tricyclo [3.3.1.1^3.7] decane-1-amine-3,5-dimethylhydrochloride

Structure:

Molecular formula: \( \text{C}_{12}\text{H}_{22}\text{NCl} \)
Molecular weight: 215.77 g/mol
Appearance: White to off-white powder.
Solubility: Soluble in water and in methanol.

Memantine hydrochloride is the subject of an active substance master file (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.
An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate robust, stable, film-coated tablets, bioequivalent to Ebixa 5, 10, 15 and 20 mg Film-coated tablets (H.Lundbeck A/S).

Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory. The Marketing Authorisation holder has committed to performing process validation studies on future full scale production batches.

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 2 years with storage conditions “Do not store above 25°C” and “Keep the blister in the outer carton in order to protect from light” have been set. These are satisfactory.

Suitable post approval stability commitments have been provided.

II.3 Discussion on chemical, pharmaceutical and biological aspects
The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of memantine hydrochloride are well known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.
A suitable justification has been provided for not submitting an environmental risk assessment. As these products are intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of these products from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

For these generic applications, the Applicant applied for Biopharmaceutics Classification System (BCS) based biowaiver for all strengths. A bioequivalence (BE) study on the 20 mg strength was also submitted as supportive data only.

With the exception of one bioequivalence study, no new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 BCS Biowaiver

The Applicant applied for Biopharmaceutics Classification System (BCS) based biowaiver for all tablet strengths. In line with the ‘Note for Guidance on the investigation of bioavailability and bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), this was considered acceptable as memantine hydrochloride is highly soluble with complete absorption, high permeability (BCS class I) and is not considered to be a narrow-therapeutic drug. Comparative dissolution profiles were provided for each strength of the test and reference products and similarity of dissolution profiles confirmed. There are differences in the composition between the test and reference product, but these were not considered to affect the bioavailability of the products.

IV.3 Pharmacokinetics

One bioequivalence study under fasting conditions, with the 20 mg formulation:

This is an open-label, randomised, two-period, two-treatment, two-sequence, crossover, single dose bioequivalence study comparing the pharmacokinetics of the test product Memantine Hydrochloride 20 mg Tablets (Lupin Limited) with the reference product Ebixa (Memantine Hydrochloride) 20 mg tablets (H.Lundbeck A/S) in 28 healthy adult subjects, under fasting conditions.

Blood samples were collected at pre-dose and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours post dose. The washout period was 21 days.

<table>
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<tr>
<th>PK Parameter</th>
<th>Geometric Least Square Mean</th>
<th>90% Confidence Interval (T/R)</th>
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<tbody>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td>Test (T)</td>
<td>Reference (R)</td>
</tr>
<tr>
<td>24.622</td>
<td>24.614</td>
<td>100.03</td>
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<tr>
<td>AUC(_{72}) (ng.hr/ml)</td>
<td>Test (T)</td>
<td>Reference (R)</td>
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<tr>
<td>1247.870</td>
<td>1226.081</td>
<td>101.78</td>
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The 90% confidence intervals for C\(_{\text{max}}\) and AUC\(_{72}\) were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Memantine Hydrochloride 20 mg Tablets) and the reference formulation (Ebixa 20 mg tablets) under fasting conditions.

IV.4 Pharmacodynamics

No new data have been submitted and none are required for applications of this type.
IV.5 Clinical efficacy
No new data on efficacy have been submitted and none are required for this type of applications.

IV.6 Clinical safety
No new safety data were submitted and none are required.

IV.7 Risk Management Plan (RMP)
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to YMANA 5, 10, 15 and 20 mg Film-coated Tablets.

Summary table of Safety concerns

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
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<tr>
<td>Important identified risks</td>
<td>Drug hypersensitivity;</td>
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<td>Hallucinations, psychotic reactions;</td>
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<td>Seizures;</td>
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<td>Cardiac failure;</td>
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<td>Venous thrombosis/thromboembolism;</td>
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<td>Dyspnoea;</td>
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<td>Pancreatitis;</td>
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<td>Concomitant administration with amantadine, ketamine, dextromethorphan;</td>
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<td>Factors that may raise urine pH;</td>
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<td>Hepatic disorders.</td>
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<td>Important potential risks</td>
<td>Prostate cancer;</td>
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<td>Epilepsy;</td>
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<td>Depression, suicidal ideation and suicide.</td>
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<tr>
<td>Important missing information</td>
<td>Recent myocardial infarction and uncompensated congestive heart failure (NYHA III-IV), or</td>
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<td>uncontrolled hypertension;</td>
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<td></td>
<td>Patients with severe hepatic impairment.</td>
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</table>
### Summary table of risk minimisation measures

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| **Drug hypersensitivity**                  | - Proposed text in SmPC (Listed as undesirable effects in 4.8.)  
  - Collection, evaluation, recording and reporting of all ICSR;  
  - Literature monitoring (worldwide and local) for safety issues associated with memantine;  
  - Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;  
  - Active follow up of all hypersensitivity cases associated with memantine administration;  
  - Liaison with regulatory authorities                                                                                                                   | N/A                                   |
| **Hallucinations, Psychotic reactions**    | - Proposed text in SmPC (Listed as undesirable effects in 4.8.)  
  - Collection, evaluation, recording and reporting of all ICSR;  
  - Literature monitoring (worldwide and local) for safety issues associated with memantine;  
  - Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;  
  - Active follow up of all cases with Hallucinations, Psychotic reactions associated with memantine administration;  
  - Liaison with regulatory authorities                                                                                                                   | N/A                                   |
| **Seizures**                                | - Proposed text in SmPC (Listed as undesirable effects in 4.8.)  
  - Collection, evaluation, recording and reporting of all ICSR;  
  - Literature monitoring (worldwide and local) for safety issues associated with memantine;  
  - Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;  
  - Active follow up of all cases with Seizures associated with memantine administration;                                                                | N/A                                   |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Proposed text in SmPC (Listed as undesirable effects in 4.8.)</th>
<th>Collection, evaluation, recording and reporting of all ICSR;</th>
<th>Literature monitoring (worldwide and local) for safety issues associated with memantine;</th>
<th>Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;</th>
<th>Active follow up of all cases with cardiac failure associated with memantine administration;</th>
<th>Liaison with regulatory authorities</th>
<th>N/A</th>
</tr>
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<tbody>
<tr>
<td>Cardiac failure</td>
<td>- Proposed text in SmPC (Listed as undesirable effects in 4.8.)</td>
<td>- Collection, evaluation, recording and reporting of all ICSR;</td>
<td>- Literature monitoring (worldwide and local) for safety issues associated with memantine;</td>
<td>- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;</td>
<td>- Active follow up of all cases with cardiac failure associated with memantine administration;</td>
<td>- Liaison with regulatory authorities</td>
<td>N/A</td>
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<tr>
<td>Venous Thrombosis, thromboembolism</td>
<td>- Proposed text in SmPC (Listed as undesirable effects in 4.8.)</td>
<td>- Collection, evaluation, recording and reporting of all ICSR;</td>
<td>- Literature monitoring (worldwide and local) for safety issues associated with memantine;</td>
<td>- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;</td>
<td>- Active follow up of all cases with Venous Thrombosis, thromboembolism associated with memantine administration;</td>
<td>- Liaison with regulatory authorities</td>
<td>N/A</td>
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<tr>
<td>Dyspnoea</td>
<td>- Proposed text in SmPC (Listed as undesirable effects in 4.8.)</td>
<td>- Collection, evaluation, recording and reporting of all ICSR;</td>
<td>- Literature monitoring (worldwide and local) for safety issues associated with memantine;</td>
<td>- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;</td>
<td>- Active follow up of all dyspnoea cases associated with memantine administration;</td>
<td>- Liaison with regulatory authorities</td>
<td>N/A</td>
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<tr>
<td>Pancreatitis</td>
<td>- Proposed text in SmPC (Listed as undesirable effects in 4.8.)</td>
<td>- Collection, evaluation, recording and reporting of all ICSR;</td>
<td>- Literature monitoring (worldwide and local) for safety issues associated with memantine;</td>
<td>- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;</td>
<td>- Active follow up of all pancreatitis cases associated with memantine administration;</td>
<td>- Liaison with regulatory authorities</td>
<td>N/A</td>
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<tr>
<td>Condition</td>
<td>Description</td>
<td>Reference</td>
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</table>
| Concomitant administration with amantadine, ketamine, dextromethorphan   | - Liaison with regulatory authorities  
- Proposed text in SmPC (Warning in 4.4; Interactions in 4.5.).  
- Collection, evaluation, recording and reporting of all ICSR;  
- Literature monitoring (worldwide and local) for safety issues associated with memantine;  
- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;  
- Active follow up of all cases associated with this combination;  
- Liaison with regulatory authorities | N/A             |
| Factors that may raise urine pH                                           | Proposed text in SmPC (Warning in 4.4; Pharmacokinetics in 5.2.)                                                                                                                                              | N/A             |
| Hepatic disorders                                                         | - Proposed text in SmPC (Warning in 4.2; Listed as undesirable effects in 4.8).  
- Collection, evaluation, recording and reporting of all ICSR;  
- Literature monitoring (worldwide and local) for safety issues associated with memantine;  
- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;  
- Active follow up of all cases of hepatic disorders associated with memantine;  
- Liaison with regulatory authorities | N/A             |
| Prostate cancer                                                           | - Collection, evaluation, recording and reporting of all ICSR;  
- Literature monitoring (worldwide and local) for safety issues associated with memantine;  
- Conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals;  
- Active follow up of all prostate cancer cases;  
- Liaison with regulatory authorities | N/A             |
| Epilepsy                                                                  | Proposed text in SmPC (Warning in 4.4.)                                                                                                                                                                      | N/A             |
| Depression, suicidal ideation and suicide                                 | Proposed text in SmPC.  
Listed as undesirable effects in 4.8.                                                                                                                                                                         | N/A             |
| Recent myocardial infarction and Uncompensated congestive heart failure   | Proposed text in SmPC  
Notification for missing information in in 4.4.                                                                                                                                                           | N/A             |
| (NYHA III-IV), or uncontrolled hypertension                              |                                                                                              |                 |
| Patients with severe hepatic impairment                                   | Proposed text in SmPC  
Notification for missing information in 4.2                                                                                                                                                                 | N/A             |
IV.8 Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V User consultation
User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Memantine Lupin 5, 10, 15 and 20 mg film-coated Tablets (LUPIN (Europe) Ltd). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with memantine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Annex 1 – Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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