PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Xapimant 10 mg and 20 mg, film-coated tablets
Xapimant 10 mg/ml, oral solution
Sandoz B.V., the Netherlands

memantine (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2682/001-003/DC
Registration number in the Netherlands: RVG 112085-112087

12 August 2013

Pharmacotherapeutic group:	psychoanaleptics, anti-dementia drugs
ATC code:	N06DX01
Route of administration:	oral
Therapeutic indication:	treatment of patients with moderate to severe Alzheimer's disease
Prescription status:	prescription only
Date of authorisation in NL:	2 July 2013
Concerned Member States:	Decentralised procedure with: EE, LT, PL, RO, SI, SK; 10 mg tablets and 10 mg/ml oral solution only - BG
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Xapimant 10 mg and 20 mg, film-coated tablets and Xapimant 10 mg/ml, oral solution from Sandoz B.V. The date of authorisation was on 2 July 2013 in the Netherlands.

The product is indicated for treatment of patients with moderate to severe Alzheimer's disease.

A comprehensive description of the indications and posology is given in the SPC.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Ebixa 10 mg and 20 mg, film-coated tablets and Ebixa 5 mg/pump actuation, oral solution (initially registered as Ebixa 10 mg/g oral drops, solution), which have been registered in the EEA since 15 May 2002 by H. Lundbeck A/S through centralised procedure EMEA/H/C/000463.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Ebixa 10 mg and 20 mg, film-coated tablets registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is memantine hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is freely soluble in water, slightly soluble in toluene at room temperature, sparingly soluble in cold toluene, soluble in 1% hydrochloric acid and in 1% phosphoric acid. Two asymmetric atoms of carbon are present in the molecule. Since there is a plane of symmetry between the two chiral centres, memantine is not a chiral molecule.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
A general description of the manufacturing process of both suppliers has been provided. The detailed manufacturing description is included in the restricted parts of the ASMFs and is adequately described. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the applicant. In general, the specification is acceptable in view of the route of synthesis and the various European guidelines.
Sufficient batch analytical data demonstrating compliance with the drug substance specification have been provided from both manufacturers.

Stability of drug substance
For the first manufacturer, stability data on the active substance have been provided for four production-scale batches stored at 25°C/60% RH (max. 60 months) and 40°C/75% RH (6 months). No trends were observed. The re-test period of 5 years (60 months), given the available data this is considered to be acceptable.
For the second supplier, data for three full-scale batches stored at 25°C/60% RH (max. 36 months) and 40°C/75% RH (6 month) has been provided. No changes were observed. The storage conditions (no special storage conditions required) can be granted as the substance is not sensitive to light. The proposed re-test period of three years can be granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product – film-coated tablets

Composition

Xapimant 10 mg is a white, oval film-coated tablet with a breaking line on both sides. The tablet can be divided into equal halves.
Xapimant 20 mg is a light red, round film-coated tablet with two crossed breaking lines on one side. The tablet can be divided into equal quarters.

The film-coated tablets are packed in transparent PVC-Aclar/Aluminium blisters, transparent PVC-PVDC/Aluminium blisters or HDPE bottles with PP screw cap with tamper-evident ring and desiccant.

The excipients are:
10 mg tablet –
Tablet core: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate
Tablet coating: hypromellose (E464), lactose monohydrate, macrogol, triacetin, titanium dioxide (E 171)

20 mg tablet –
Tablet core: lactose monohydrate, sodium starch glycolate (type A), microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate
Tablet coating: polyvinyl alcohol, macrogol, titanium dioxide (E 171), talc, iron oxide red (E172), iron oxide yellow (E172).

The composition of the two strength is not dose proportional.

Pharmaceutical development
In general the development of the product has been adequately described, the choice of excipients is justified and their functions explained. Memantine HCl tablets are a generic form of the marketed tablet named Ebixa. The qualitative composition of the 10 mg tablet and 20 mg tablet is slightly different and also not similar to the reference product Ebixa. This is due to a recent formulation change of the innovator product. Dissolution data is provided that showed similarity between the current Ebixa product and the used reference product. The provided dissolution profiles on the test product and the reference product as per previous formulation are similar and complied with the standard of NLT 85% (Q) within 15 minutes. Comparative dissolution studies at various pH values of the batches used in the bioequivalence studies have been conducted. Uniformity of mass of subdivided tablets is demonstrated. The provided data on the pharmaceutical development is considered sufficient.

Manufacturing process
The manufacturing process is a standard, straightforward manufacturing process: mixing of the excipients followed by direct compression, coating and packaging.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data or a process validation protocol on the product has been presented for full-scale batches of both strengths for all manufacturing sites. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches has been performed and demonstrated that the manufacturing process is suitable for consistently producing a drug product that meets the specifications.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable, functionality related characteristics are discussed.

Quality control of drug product
The product specification includes tests for appearance, dimensions, average mass, dissolution, identification of memantine, assay, uniformity of dosage units, purity, microbiological contamination and identification of titanium dioxide/iron oxide and chloride. A test on water content is not included, but this is justified. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production sites have been provided on several full-scale batches of each strength from all sites, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for several full-scale batches stored at 25°C/60% RH (6-48 months), 30°/65% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the stability guideline. The batches were stored in PVC-Aclar/alu-blisters, PVDC-PVC/alu blisters and HDPE bottles. No changes were observed. A photostability study was conducted; the results demonstrate that the product is photostable. Dose dispensing for the HDPE bottle has been studied. The claimed shelf-life of 48 months for the 10 mg product can be granted given the data available. The claimed shelf-life of 24 months for the 20 mg product can granted based on 12 months stability data. The claimed storage conditions (no special ones) are considered to be acceptable. The in-use period for the 10 mg and 20 mg product (6 months) in the HDPE bottle is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A declaration with respect to the TSE safety of Lactose monohydrate has been included. The lactose used can be considered to be of no risk with respect to transmitting TSE.

Medicinal Product – oral solution

Composition
Xapimant 10 mg/ml is a colourless and clear oral solution.

The oral solution is packed in amber glass bottles type III closed with a HDPE screw cap with tamper-evident ring. The bottle is packed in a carton box together with a 2 ml oral syringe (LDPE and PS) connected to a press-in bottle adapter (LDPE). The oral syringe has a main graduation in steps of 0.5 ml and 5 mg (0.5, 1, 1.5 2 ml respectively 5, 10, 15, 20 mg) and a fine graduation in steps of 0.1 ml (= 1 mg).

The excipients are: potassium sorbate, liquid (non crystallising) sorbitol (E420), sodium hydroxide (for pH adjustment), hydrochlorid acid (for pH adjustment), purified water.

Pharmaceutical development
In general the development of the product has been adequately described, the choice of excipients is justified and their functions explained. The primary packaging material used, *i.e.* amber glass bottle, dropper and screw cap, are suitable for non-sterile pharmaceutical solutions. Memantine HCl oral solution is a generic form of the marketed oral solution named Ebixa. The excipients are chosen based on the original formulation of the innovator product Ebixa. The qualitative composition is similar. Sorbitol is used in a 10% lower concentration. Its use and its concentration have been adequately justified in view of a biowaiver. The amount of preservative potassium sorbate has been demonstrated and is similar to the reference product. Although the reference product is an oral solution, administered in 5 mg/pump actuations (0.5 ml/actuation) and the proposed product is an oral solution, administered in 0.5, 1.0, 1.5, and 2.0 ml. The difference in pharmaceutical presentation has been justified and is acceptable. The product is able to dose the required 5, 10, 15 and 20 mg as 0.5, 1, 1.5 and 2.0 ml, respectively. The provided data on the pharmaceutical development is considered sufficient.

Manufacturing process
The manufacturing process is a standard, straightforward manufacturing process: preparation of the bulk followed by filtration and filling. Validation data on the manufacturing process has not been included. A validation scheme has been provided. As the MAH has evaluated the process for critical parameters, it is considered acceptable, and in line with the Note for Guidance on Process Validation (CPMP/QWP/848/96), that validation data is not included in the submission.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable, functionality related characteristics are discussed.

Quality control of drug product
The product specification includes tests for colour, appearance, pH-value, uniformity of mass of delivered doses from multidose containers, identification of memantine and of potassium sorbate, assay

(memantine and potassium sorbate), related substances, and microbiological contamination. The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two production-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the stability guideline. The batches were stored in amber glass bottles. No changes were observed. The claimed shelf-life of 48 months can be granted given the data available. The claimed storage conditions (no special ones) are considered to be acceptable. . The protocol for in-use stability study is acceptable. No changes were seen after 6 months of storage and the proposed in-use storage of 6 months is acceptable.

II.2 Non-clinical aspects

These products are generic formulations of Ebixa film-coated tablets and Ebixa 5 mg/pump actuation, oral solution, which are available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of memantine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Memantine is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Xapimant 10 mg and 20 mg film-coated tablets (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Ebixa 10 mg and 20 mg film-coated tablets (Lundbeck GmbH, Germany).

The choice of the reference products
The choice of the reference products in the bioequivalence studies is justified, as these are registered in the EEA through a centralised procedure.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 10 mg film-coated tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy male subjects, aged 23-53 years. Each subject

received a single dose (10 mg) of one of the 2 memantine formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 24, 48 and 72 hours after administration of the products.

The procedures followed for a fasted condition and a wash-out period of 35 days (*i.e*. at least 5 terminal half-lives to exclude carry-over effects) are appropriate. Therefore the study design is acceptable.

Results
Thirteen subjects completed the study. One subject was excluded prior to first study drug administration due to positive cotinine test and 2 subjects were withdrawn after Period I due to adverse events (AE). The data of 13 subjects were included in the pharmacokinetic and statistical analysis

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of memantine under fasted conditions.

Treatment N=13	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	550.4 ± 33.1	11.97 ± 1.0	7 (2 – 10)
Reference	560.2 ± 30.1	12.04 ± 0.9	7 (4 – 12)
***Ratio (90% CI)**	0.98 (0.97 – 1.00)	1.03 (0.98 – 1.09)	--
CV (%)	2.2	2.7	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life			

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. A truncated AUC is acceptable since memantine has a long half-life (60-100 hours). Based on the pharmacokinetic parameters of memantine under fasted conditions, it can be concluded that Xapimant 10 mg film-coated tablets and Ebixa 10 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
There were a total of 13 treatment-emergent adverse events (TEAEs, 10 mild and 3 moderate): 10 were related to test (6) and reference (4) drug while 3 were not suspected to be related to study medication. The most commonly TEAEs reported were somnolence and headache. Memantine is known to cause such AEs. There were no deaths, serious or significant adverse events reported during the course of the study. Overall, the test and reference drugs were well tolerated.

Bioequivalence study II – 20 mg film-coated tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy male subjects, aged 22-43 years. Each subject received a single dose (20 mg) of one of the 2 memantine formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 38 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 24, 48 and 72 hours after administration of the products.

The procedures followed for a fasted condition and a wash-out period of 38 days (*i.e*. at least 5 terminal half-lives to exclude carry-over effects) are appropriate. Therefore the study design is acceptable.

Results
Seventeen subjects were enrolled in the study. One subject withdrew his informed consent before Period 1; sixteen subjects were dosed. Thirteen subjects completed the study. Three did not report on the start of Period II and were hence withdrawn from the study. The data of 13 subjects were included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of memantine under fasted conditions.

Treatment N=13	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1347 ± 167	29.16 ± 5.2	7.5 (2 – 10)
Reference	1382 ± 197	29.30 ± 5.5	7.5 (2 – 12)
***Ratio (90% CI)**	0.98 (0.95 – 1.01)	0.99 (0.96 – 1.04)	--
CV (%)	3.9	5.8	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. A truncated AUC is acceptable since memantine has a long half-life (60-100 hours). Based on the pharmacokinetic parameters of memantine under fasted conditions, it can be concluded that Xapimant 20 mg film-coated tablets and Ebixa 20 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
No adverse event has been reported during conduct of the study.

Memantine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of memantine. Therefore, a food interaction study is not deemed necessary. Conducting bioequivalence studies under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Biowaiver
A biowaiver for Xapimant 10 mg/ml oral solution was applied for. This is acceptable, since the concentration of the medicinal product is the same as that of the reference product Ebixa 5 mg/pump

actuation, oral solution (initially registered as Ebixa 10 mg/g oral drops/solution), the excipients included do not affect gastrointestinal tract absorption or *in vivo* stability
The small difference in amount of sorbitol between innovator and generic (about 10%) is not considered to result in a difference in the rate and extent of absorption of memantine, which is classified as a BCS class I drug. In addition, as shown by the innovator, bioequivalence was established between sorbitol containing oral drops/solution and sorbitol free film-coated tablets. Therefore, the difference in sorbitol content is acceptable.
A biowaiver for the 10 mg/ml oral solution has been granted.

Risk management plan
Memantine was first approved in 2002, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of memantine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Ebixa.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 11 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Between the first and the second round several recommendations of participants of the test have been applied which led to this final version of the PL.
Although the outcome of the readability testing itself does not raise a concern to readability, the PL that has been subject to readability testing should have been based on the innovator PL of Ebixa. This was not the case. Based on the member states' comments, the MAH adapted the PL to that of Ebixa, which is appropriate.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Xapimant 10 mg and 20 mg, film-coated tablets and Xapimant 10 mg/ml, oral solution have a proven chemical-pharmaceutical quality and are generic forms of Ebixa 10 mg and 20 mg, film-coated tablets and Ebixa 5 mg/pump actuation, oral solution. Ebixa is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Xapimant 10 mg and 20 mg, film-coated tablets and Xapimant 10 mg/ml, oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 May 2013. Xapimant 10 mg and 20 mg, film-coated tablets and Xapimant 10 mg/ml, oral solution were authorised in the Netherlands on 2 July 2013.

The date for the first renewal will be: 23 May 2018.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product: film-coated tablets</u>

- The MAH committed not to market a batch until comparative dissolution profile testing in accordance with the guideline on bioequivalence has been completed. Comparative dissolution profile testing will be undertaken on the first three production batches (of the largest size).
- The MAH committed to place one production batch, provided a batch is produced, on long term stability study per year.

<u>Quality - medicinal product: oral solution</u>

- The MAH committed to include the first batch in stability studies according to ICH requirements.
- The MAH committed to perform microbial efficacy testing/in-use stability testing at the end of the planned shelf-life after 60 months.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
TEAE	Treatment-emergent Adverse Events
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached