CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Galantamine Retard Mylan 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard Mylan B.V., the Netherlands

galantamine (as hydrobromide)

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/2030/001-003/DC
Registration number in the Netherlands: RVG 107647, 107649-107650

25 January 2012

Pharmacotherapeutic group:	anti-dementia drugs, anticholinesterases
ATC code:	N06DA04
Route of administration:	oral
Therapeutic indication:	symptomatic treatment of mild to moderately severe dementia of the Alzheimer type
Prescription status:	prescription only
Date of authorisation in NL:	14 November 2011
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, EL, ES, FI, FR, LU, PT, SE, SI, SK, UK
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 Galantamine Retard Mylan 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard from Mylan B.V. The date of authorisation was on 14 November 2011 in the Netherlands.

The product is indicated for symptomatic treatment of mild to moderately severe dementia of the Alzheimer type. A comprehensive description of the indications and posology is given in the SPC.

Galantamine, a tertiary alkaloid is a selective, competitive and reversible inhibitor of acetylcholinesterase. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. As a result, an increased activity in the cholinergic system associated with improved cognitive function can be achieved in patients with dementia of the Alzheimer type.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Reminyl 8, 16 and 24 mg, prolonged-release capsules marketed by Jansen Cilag, Johnson & Johnson, and Shire. The first Reminyl authorisation in the EEA concerned 4 mg, 8 mg and 12 mg *film-coated tablets*, registered in Sweden by Janssen-Cilag AB since 1 March 2000.
In the Netherlands, Reminyl Retard Capsules 8 mg, 16 mg and 24 mg (NL Licence RVG 31372-13174) have been authorised since 1 December 2004 through MRP SE/H/0210/005-007. In addition, reference is made to Reminyl Retard authorisations in the individual member states (reference product).

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 initially submitted as report one multiple-dose bioequivalence study under fasted conditions with Galantamine Retard Mylan 24 mg prolonged-release capsules versus Reminyl XL 24 mg capsules, obtained from the UK. One steady-state study in support of the application for this prolonged-release (PR) formulation with several strengths was considered insufficient. In addition, a single-dose study under fasting and fed conditions was requested. As a response the MAH submitted three new BE studies with the UK reference product Reminyl XL: a single-dose study with the 8 mg capsule under fed and fasting conditions, and a steady-state study with the 8 mg capsule. 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. This generic product can be used instead of its reference product.

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 galantamine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white powder, which is soluble in water, insoluble in alcohol and acetone. Galantamine has three asymmetric centres. The polymorphic form of galantamine hydrobromide is studied by X-Ray diffraction.

The Active Substance Master File (ASMF) procedure is used for 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
The manufacturing process has been described in sufficient detail. Acceptable specifications are included for the starting materials, reagents and solvents. The structure has been adequately elucidated.

Quality control of drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to galantamine hydrobromide are of sufficient quality in view of the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up. Batch analytical data demonstrating compliance with the specifications have been provided on three batches.

Stability of drug substance
Stability studies under long term conditions (25°C/60% RH) for 36 month and accelerated (40°C/75% RH) conditions for six month have been performed on four pilot-scale batches. No significant changes were observed for any of the tested parameters throughout storage.
On the basis of the presented data, a retest period of three years has been accepted for galantamine hydrobromide.

** 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

Composition
Galantamine Retard Mylan 8 mg is a size 2 hard gelatin capsule with a white body and pink cap printed in black ink 'MYLAN' over 'GT8' on the body and the cap.
Galantamine Retard Mylan 16 mg is a size 2 hard gelatin capsule with a white body and pale pink cap printed in black ink 'MYLAN' over 'GT16' on the body and the cap.
Galantamine Retard Mylan 24 mg is a size 1 hard gelatin capsule with a white body and pink cap printed in black ink 'MYLAN' over 'GT24' on the body and the cap.

The hard capsules are packed in PVC/PE/PVdC Aluminium blisters, Aluminium/Aluminium blisters, a polypropylene tablet container with polyethylene lid and silica gel desiccant (Securitainer) or an HDPE bottle with polypropylene child resistant cap and silica gel desiccant.

The excipients are:
Capsule content - polyvinyl acetate, colloidal anhydrous silica, povidone, hydrogenated vegetable oil, magnesium stearate, sodium lauryl sulphate.
Capsule shell - gelatin, titanium dioxide (E171), Allura Red AC (E129), titanium dioxide (E171), gelatin, shellac, propylene glycol, potassium hydroxide, black iron oxide (E172).

The three strengths of galantamine capsules are directly scaled.

Pharmaceutical development
The dosage form consists of prolonged-release matrix tablets in a capsule. It was decided to develop 8 mg prolonged release tablets and to then encapsulate 1, 2 or 3 tablets. The choice of dosage form design and manufacturing process has been sufficiently justified. The dissolution profile of these encapsulated tablets was determined and assessed against Reminyl XL prolonged-release capsules. The results showed comparable dissolution profiles. The formulation development has been adequately performed.
The MAH demonstrated the similarity between the Galantamine prolonged release capsules 8 mg, 16 mg and 24 mg based on the same composition and the comparative dissolution profiles of the different strength of tablets in four different media.

Manufacturing process
The manufacturing process consists of dry granulation, sieving, blending, compression and encapsulation. This is considered to be a non-standard process because it concerns an extended-release capsule. The manufacturing process has been adequately described. Sufficient in-process controls have been laid down.
Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipients
All excipients used comply with their Ph.Eur. monographs with the exception of Kollidon SR and the gelatine capsule shells, which are controlled to the supplier's in-house specification, and hydrogenated vegetable Oil type 1, which is controlled in accordance with BP or USNF. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, dissolution, uniformity of dosage units, related substances, assay, microbial purity and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Validations of the analytical methods have been presented. Analytical data from two batches of 8 mg capsules and one batch of 16 and 24 mg capsules each have been presented. The batch analysis results show that the finished products meet the specifications.

Stability of drug product
Stability testing of the finished product was carried out with two batches of 8 mg capsules and one batch each for 16 mg and 24 mg capsules in each package (bulk shipment pack, PVC/PE/PVdC-Al blisters, Al-Al blisters, securitainers and HDPE bottles) under long-term conditions (25°C/60% RH) and intermediate (30°C/65% RH) up to 24 months and under accelerated (40°C/75% RH) conditions for six months. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
Significant change for dissolution was observed for several batches of each strength packed in PVC/PE/PVdC-Al blister packs at accelerated storage conditions at 12 weeks and at intermediate storage conditions (30°C/65%RH) at 6, 9 and 12 months.

Additional testing at intermediate storage conditions (30°C/65%RH) was conducted on these batches and results of up to 12 months storage were presented. However, dissolution results were out of specification at 9 and 12 months at 30°C/65%RH.
Based on the results of the 16 mg and 24 mg strengths, accelerated studies were not initiated for the 8 mg strength. An out-of-specification result for dissolution was observed for one batch packed in blister at intermediate storage conditions after 6 months. Stability testing at long term (25°C/60%RH) for 24 months demonstrated no trends or out-of-specification results. As the product was established to be stable for all three strengths at testing conditions of 25°C/60%RH, the applicable storage condition is "Do not store above 25°C".
No significant change was observed in galantamine 16 mg and 24 mg capsules packed in securitainers upon 6 months storage at accelerated conditions and 24 months storage at long term conditions. However, an out-of-specification result for dissolution was observed for one 8 mg batch at accelerated storage conditions at 6 months. Additional testing at the intermediate storage conditions was conducted on this batch. Results up to 9 months were presented and found to be acceptable.
No significant change was observed for any strength of galantamine capsules packed in HDPE bottles or Al-Al blisters upon 6 months storage at accelerated conditions and 24 months storage at long-term conditions.
A photostability study in accordance with the Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products has been performed on one batch of each strength of galantamine hydrobromide extended release capsules. The samples were tested in accordance with the stability specifications and test methods. All parameters tested during the photostability studies remained unchanged.
An "open pot" stability study (in-use stability study) was conducted with one batch of each strength in open securitainers at 25°C/60%RH for 12 weeks. The results show that the capsules are remained unchanged for 12 weeks under in-use conditions.
Based on the results provided, the following shelf-life has been granted for each of the packages:
PVC/PE/PVdC-Al Blister - 24 months, 'Do not store above 25°C'
Securitainer - 24 months, 'Store below 30°C'
HDPE Bottle - 36 months, no further storage condition
Al-Al blister - 36 months, no further storage condition.

Several commitments have been made with regard to the finished product; these can be found on page 11 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The starting materials magnesium stearate and gelatine are derived from animal origin. TSE certificates have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Reminyl Retard Capsules, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 galantamine 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

Galantamine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Galantamine Retard Mylan 24 mg, prolonged-release capsules (Mylan B.V., NL)

is compared with the pharmacokinetic profile of the reference product Reminyl XL 24 mg capsules (Shire Pharmaceuticals, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 24 mg steady-state
Design
This study consisted of a two-week dose escalation/titration phase, using 8 and 16 mg products from the Australian market, followed by three one-week dosing intervals for a total of 5 weeks. All 36 subjects were housed in the clinic for the duration of the study, approximately 36 days. Throughout the course of the investigation (Study Day 1 through 35), study medication was administered after a supervised overnight fast of at least 10 hours. On days 1 through 20, 22 through 27 and 29 through 34 subjects consumed breakfast two hours after dosing. Subjects also received lunch and dinner, provided at standard times throughout the study. On Study Days 21, 28 and 35, subjects fasted for 4 hours after dosing and then received a standard meal (lunch) 4 hours post-dose followed by an evening meal 10 hours after dosing. Subjects consumed 240 mL with each dose of study medication. Subjects received 240 mL of ambient temperature water beginning at 1.25 hours before dosing and 1 hours after dosing on Study Days 21, 28, and 35. Water was not permitted for 1 hour before and until 1 hour after dosing, but was allowed at all other times.
Blood samples were collected not earlier than 30 min prior to dosing on Study Days 1, 19, 20, 26, 27, 33 and 34, as well as the following times on Study Days 21, 28, 35: 0.00 (pre-dose) and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20 and 24 hours.
The primary PK variables were: AUC_{τ}, C_{max}, C_{min}. The minimum concentration at steady-state ($C_{min}(SS)$) was determined as the minimum drug concentration within the last dosing interval during steady state. Three consecutive pre-dose concentrations were determined for each 24 mg formulation. The pre-dose concentrations (CPD) were determined to assess whether steady-state has been achieved. C_{trough} as pre-dose concentration at Day 7. Fluctuation (PTF%, expressed as a percentage) was determined as the range of concentrations divided by the average steady-state concentration.

The study design is acceptable. According to the guideline on Investigation of Bioequivalence, in steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life). The build-up period for the 24 mg capsule was 7 days, thus more than 5 times the terminal half-life. However, during the titration steps the innovator product from the Australian market was used: from the regulatory perspective, the use of non-EU Reference product in a BE study was considered not acceptable. This was put forward as a major objection in the first round. The MAH has however sufficiently justified that the use of the Australian reference product did not hamper the validity of the study outcome and this issue is considered to be solved.

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

Results
Of the 36 subjects who were dosed in the study, 31 subjects (18 males and 13 females) with a mean age of 34.6 years (range = 21 to 54 years) completed the study. Two subjects were dismissed due to non-compliance. One subject withdrew for personal reasons, and two subjects withdrew due to an adverse event. The completing subjects consisted of 8 Caucasians, 6 Asians, 6 Blacks and 11 Hispanics. Pharmacokinetic and statistical analysis of the plasma galantamine data was conducted on the data from the 31 subjects who successfully completed the study.

Table 1. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=31	AUC_τ ng/ml/h	C_{max} ng/ml	C_{min} ng/ml	PTF% %
Test	1284.03 (31.10%)	83.26 (24.02%)	27.33 (51.92%)	110.36 (23.10%)
Reference	1404.47 (28.31%)	87.45 (24.44%)	30.28 (39.46%)	100.50 (15.56%)
***Ratio (90% CI)**	0.90 (0.87-0.94)	0.95 (0.92-0.98)	0.86 (0.80-0.92)	1.09 (1.04-1.14)
CV (%)	-	--	--	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

The 90% confidence intervals calculated for AUC_τ, C_{max} and C_{min} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. However, the LSMeans Ratio for C_{trough} (defined as the last measured concentration measured at the end of the dosing interval at steady-state) was 0.84 with 90% CI of 0.76–0.92. Thus, it was concluded that BE was not shown for the 24 mg capsule. However, the CHMP had meanwhile concluded for another product (EMA/H/A-29(4)/126), that for galantamine C_{min} steady-state values most adequately describe the release characteristics. The current EMA Note for guidance on modified release oral and transdermal dosage forms Section II (Pharmacokinetic and Clinical Evaluation, CMP/EWP/280/96 January 2000) recommends that the bioequivalence should be shown for AUC_τ, C_{max} and C_{min}, but it does not provide a definition for the C_{min}. Therefore, using this earlier CHMP conclusion, it was agreed that bioequivalence can be concluded for Galantamine Retard Mylan 24 mg with Reminyl XL 24 mg prolonged-release capsules based upon the 90% CI for C_{min} (defined as the minimum concentration in the whole sampling interval), which were within the 0.80-1.25 limits.

However, one steady-state study in support of the application for a prolonged-release (PR) formulation with several strengths is considered insufficient. In addition, a single-dose study under fasting and fed conditions was asked for. This was put forward as a major objection. As response to this, the MAH submitted three new BE studies: a single-dose study with the 8 mg capsule under fed and fasting conditions and a steady-state study with the 8 mg capsule. In all three studies Reminyl XL 8 mg capsules ((Shire Pharmaceuticals, UK) was used as reference product.

Bioequivalence study II – 8 mg under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 35 healthy subjects. After a supervised overnight fast of at least 10 hours, and 30 minutes before drug administration, subjects were served a standard high-fat, high calorie breakfast of between 800 to 1000 calories (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat). The breakfast consisted of two eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 128 g of hash brown potatoes, and 200 mL of whole milk. Subjects were required to completely consume this breakfast prior to drug administration. Each subject received a single dose (8 mg) of one of the 2 galantamine formulations. There were 2 dosing periods, separated by a washout period of 7 days.
Blood samples were collected pre-dose and at 1.5, 3, 3.5, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 6.5, 7, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

Results

One subject was withdrawn from the study prior to the second phase of the study due to vomiting approximately 7.25 hours post-dose. The data from 34 volunteers has been included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of galantamine under fed conditions.

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	392.60 ± 81.88	408.00 ± 87.82	24.88 ± 4.74	5.49 ± 1.15	8.58 ± 1.78
Reference	412.90 ± 91.95	424.20 ± 93.69	28.19 ± 7.76	6.81 ± 1.10	7.77 ± 1.18
***Ratio (90% CI)**	0.95 (0.93-0.98)	0.96 (0.94-0.99)	0.90 (0.86-0.94)	--	--
CV (%)	6.53	6.78	10.45	--	--

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

**ln-transformed values*

Bioequivalence study III – 8 mg under fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects. Each subject received a single dose (8 mg) of one of the 2 galantamine formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 10 hours. Fasting was continued for at least 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 14 days.
Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 6.5, 7, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

Results

All thirty-six subjects completed the study, but as per protocol only the samples from thirty-five subjects were included in the statistical analysis, as one subject was excluded due to vomiting.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of galantamine under fasted conditions.

Treatment N=35	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	390.32 ± 113.65	408.85 ± 123.74	19.14 ± 3.86	5.61 ± 2.05	9.10 ± 1.56
Reference	388.98 ± 111.50	408.93 ± 124.73	19.48 ± 5.07	5.91 ± 1.72	9.55 ± 1.75
***Ratio (90% CI)**	1.00 (0.97-1.04)	1.00 (0.96-1.04)	0.99 (0.94-1.05)	--	--
CV (%)	9.03	9.27	13.65	--	--

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

**ln-transformed values*

Bioequivalence study IV – 8 mg steady state

Design

This was a randomized, open-label, 2-way crossover bioequivalence study following a 8 mg dose daily for 5 consecutive days in 36 healthy subjects under fasted conditions.

Each volunteer received a single oral dose of galantamine 8 mg extended-release capsule daily for 5 consecutive days in each of the 2 study periods. There was a washout period of 10 days between phases. Blood samples were collected prior to drug administration on Days 3, 4, 5 and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, and 24 hours post-dose on Day 5, in each period.

Results

Two volunteers chose to withdraw from the study due to personal reasons. Thirty-four volunteers completed the study and were included in the statistical analysis as per the protocol.

Table 4. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=31	$AUC_{0-t\ ss}$ ng/ml/h	$C_{max\ ss}$ ng/ml	$C_{min\ ss}$ ng/ml	PTF% %
Test	406.75 ± 89.02	25.58 ± 4.31	8.06 ± 2.99	107.27 ± 24.21
Reference	408.35 ± 110.01	24.50 ± 5.09	8.38 ± 3.68	99.01 ± 20.64
***Ratio (90% CI)**	1.00 (0.97-1.04)	1.05 (1.01-1.09)	0.96 (0.87-1.06)	--
CV (%)	9.10	8.59	23.55	--

AUC_{τ} area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

Conclusion on BE study II, III and IV

The 90% confidence intervals calculated for AUC_{0-t}, AUC and $C_{max,}$ under both fasted and fed conditions, as well as AUC_{0-t}, C_{max} and C_{min} at steady state, are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on these pharmacokinetic parameters of galantamine, it can be concluded that Galantamine Retard Mylan 8 mg and Reminyl XL 8 mg prolonged-release capsules are bioequivalent with respect to rate and extent of absorption, and fulfil

the bioequivalence requirements for prolonged-release formulations outlined in the relevant CHMP Note for Guidance.

Biowaiver
A total of four BE studies were performed with the 8 mg and 24 mg formulations and a biowaiver was sought for the 16 mg capsules. The application concerns multiple unit formulations of a medicinal product showing linear pharmacokinetics with multiple strengths where:
- compositions of the lower strengths are proportional to that of the highest strength
- the formulation contain identical beads/tablets
- profiles are acceptable.

The results of the bioequivalence study performed with the 8 mg and 24 mg therefore apply to the 16 mg capsules as well.

Food effect
Bioequivalence was demonstrated under fed, fasted and multiple-dose conditions as is required for prolonged-release capsules to exclude dose dumping effect of food. In accordance with the reference product, the SPC states that 'Concomitant administration with food slows the absorption rate of galantamine but does not affect the extent of absorption. It is recommended that Galantamine Retard be taken with food in order to minimise cholinergic side effects.'

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).

Risk management plan
Galantamine was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of galantamine 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.
However, during the last renewal procedure for the innovator it was concluded that the following safety issues should be monitored and reported in each PSUR: QT prolongation and medication errors between IR and PR formulations. The MAH committed to monitor and reported on these issues as well.

Product information

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

Readability test
The package leaflet has been evaluated via a user consultation study. This was accepted, as the PIL is in full accordance with the innovator's, which has been successfully user tested.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Galantamine Retard Mylan 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Reminyl Retard. Reminyl Retard is a well-known medicinal product with an established favourable efficacy and safety profile.

Galantamine Retard Mylan is a prolonged release, multiple unit formulation. According to the guideline CPMP/EWP/280/96, three studies under fasting, fed and multiple dose conditions are required for prolonged-release formulations. 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 Galantamine Retard Mylan 8 mg, 16 mg and 24 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 9 August 2011. Galantamine Retard Mylan 8 mg, 16 mg and 24 mg, prolonged-release capsules, hard were authorised in the Netherlands on 14 November 2011.

Galantamine takes part in the EU Harmonised Birth Dates project of the Heads of Medicines Agencies. The first data lock point for galantamine is February 2012. The first PSUR will cover the period from August 2011 to February 2012.

The date for the first renewal will be: October 2015.

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

<u>Quality - medicinal product</u>

- The MAH committed to assess microbial purity on the first three production batches and subsequently on one batch in every ten or one batch per year.
- The MAH committed to perform process validation testing on the first three production-scale batches of each strength, to show acceptable agreement within and between batches throughout the manufacturing process.
- The MAH committed to perform stability studies on the first three commercial batches of each strength.

<u>Pharmacovigilance</u>

- The MAH committed to monitor for and report on QT prolongation and medication errors between IR and PR formulations.

List of abbreviations

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
PR	Prolonged-release
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
7USP	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
Change in the name of the medicinal product in Belgium.	NL/H/2030/IB/002/G	IB/G	1-12-2011	17-1-2012	Approval	N