CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levodopa/Carbidopa Mylan 100/10 mg, 100/25 mg and 250/25 mg tablets
Mylan B.V., the Netherlands

levodopa / carbidopa

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/2357/001-003/DC
Registration number in the Netherlands: RVG 110060 - 110062

10 April 2013

Pharmacotherapeutic group:	anti-Parkinson drugs, dopaminergic agents, levodopa and decarboxylase inhibitor
ATC code:	N04BA02
Route of administration:	oral
Therapeutic indication:	treatment of Parkinson's disease
Prescription status:	prescription only
Date of first authorisation in NL:	19 November 2012
Concerned Member States:	Decentralised procedure with NL/H/2357/001/DC: FR NL/H/2357/002/DC: CZ, DE, IT, PL and PT NL/H/2357/003/DC: CZ, FR, IT, PL and PT
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 Levodopa/Carbidopa Mylan 100/10 mg, 100/25 mg and 250/25 mg tablets, from Mylan B.V. The date of authorisation was on 19 November 2012 in the Netherlands.

The product is indicated for the treatment of Parkinson's disease.

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

Levodopa is the metabolic precursor of dopamine, and is given as replacement therapy in Parkinson's disease. Dopamine is severely depleted in the striatum, pallidum and substantia nigra of Parkinsonian patients and it is considered that administration of levodopa raises the level of available dopamine in these centres. However, conversion of levodopa into dopamine by the enzyme dopa decarboxylase also takes also place in extracerebral tissues. As a consequence the full therapeutic effect may not be obtained and side-effects occur.
Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of levodopa can be used, reducing the incidence and severity of peripheral side effects. Carbidopa, in conjunction with levodopa has significant advantages; these include reduced gastro-intestinal side effects, a more rapid response at the initiation of therapy and a simpler dosage regimen.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sinemet 110, 125 and 275 tablets (NL License RVG 06706, 08740, 06707) which has been registered in the Netherlands by Merck Sharp & Dohme B.V. since 1974 (100/10 mg and 250/25 mg) and 1980 (100/25 mg). In addition, reference is made to Sinemet authorisations in the individual member states.

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 products are compared with the pharmacokinetic profile of the reference products Sinemet 125 and 275 tablets, registered in Italy. 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
Levodopa
The active substance levodopa is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to off-white crystalline powder which is slightly soluble in water. Levodopa contains one chiral centre. The drug substance is the pure S enantiomer. No polymorphism has been reported.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur, USP and CEP, with additional requirements for ethanol and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance
The active substance is stable for 36 months when stored in a two-layer polyethylene bag placed in a fibre drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Carbidopa
The active substance is carbidopa, an established active substance described in the Ph.Eur. The active substance is a white to creamy powder which is slightly soluble in water. Carbidopa contains one chiral centre. The drug substance is the pure S enantiomer. No polymorphism has been reported.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur and CEP, with additional requirements for residual solvents and particle size distribution. The specification is acceptable in view of the route of

synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored protected from light in double polyethylene bags kept in fibre drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Levodopa/Carbidopa Mylan 100/10 mg are blue, 7.94 mm round, flat-faced, beveled edge tablets debossed with 'M' above the score line and 'CL1' below the score line on one site of the tablet and blank on the other side.
Levodopa/Carbidopa Mylan 100/25 mg are yellow, 7.94 mm round, flat-faced, beveled edge tablets debossed with 'M' above the score line and 'CL2' below the score line on one side of the tablet and blank on the other side.
Levodopa/Carbidopa Mylan 250/25 mg are blue, 10.32 mm round, flat-faced, beveled edge tablets debossed with 'M' above the score line and 'CL3' below the score line on one side of the tablet and blank on the other side.

The 10/100 mg tablets are dose proportional to the 25/250 mg tablets.

The 100/25 mg and 250/25 mg strength tablets can be divided into equal doses. The score line on the 100/10 mg strength tablets is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses. For the 100/25 mg and 250/25 mg strength tablets the MAH demonstrated compliance to the requirements of the Ph.Eur. for subdivision of 100/25 mg and 250/25 mg tablets.

The tablets are packed in PVC-PE-PVdC/Aluminium clear film blister strips containing 20, 30, 50, 60, 100, 200 or 600 tablets, or in high density polyethylene bottles with polyprolylene cap containing 100 or 500 tablets.

The excipients are:
100/10 mg and 250/25 mg tablets: hydroxypropyl cellulose, pregelatinised starch (maize), cellulose microcrystalline, crospovidone, magnesium stearate and indigo carmine aluminium lake (E132).
100/25 mg: hydroxypropyl cellulose, pregelatinised starch (maize), cellulose microcrystalline, crospovidone, magnesium stearate and quinoline yellow aluminium lake (E104).

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials. Formulation trials were performed to investigate the effect of binder level, grade and level of microcrystalline cellulose, disintegrate level and the addition of magnesium stearate on flow properties, sticking, capping and dissolution rate. The choice of manufacturing process and packaging has been adequately justified.
The batches (250/25 mg and 100/25 mg) used in the bioequivalence studies have the same composition and are manufactured in the same way as the future commercial batches. The BE batch is of sufficient size in relation to the intended commercial batch size. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is divided into three steps wet granulation, blending and compression. The product is manufactured using conventional manufacturing techniques. Adequate process validation data of two pilot batches of each strength has been provided. The out of specification results for assay and content uniformity of one batch (100/10 mg) has been adequately discussed. Process validation for batches of the maximum production scale will be performed post authorisation.

Control of excipients
The excipients comply with relevant Ph.Eur. monographs, except for indigo carmine AL and quinoline yellow AL which comply with the in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, dissolution, uniformity of dosage units, assay, related substances, water content and microbial contamination. The drug product 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 pilot scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two pilot scale batches of each strength stored at 25°C/60% RH (12 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear PVC-PE-PVdC/Aluminium blisters and beige HDPE containers. Increases were observed in related substances (blister and bottle) and water content (blister). Furthermore a decrease in hardness was observed (blister and bottle). All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits.
Photostability studies have been performed on one batch of each strength in accordance with NfG on the Photostability Testing of New active substances and Medicinal Products. The tablets were directly exposed. No changes were observed in description, assay and related substances. Based on the stability data provided a shelf life of 24 months without special storage conditions can be granted.
In use stability data has been provided demonstrating that the product remains stable for 6 months following first opening of the container, when stored at long term conditions. Based on the in-use stability data a declaration of an in-use shelf life is not considered necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, magnesium stearate is of vegetable origin. A theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Sinemet 110, 125 and 275 tablets, which is 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 levodopa and carbidopa 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

Levodopa and carbidopa are well-known active substances 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 Board 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 product Levodopa/Carbidopa Mylan 100/25 mg and 250/25 mg tablets is compared with the pharmacokinetic profile of the reference product Sinemet 125 and 275 tablets.

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.

Study I, 100/25 mg formulation
Design
A two-way cross over bioequivalence study was carried out under fasted conditions in 44, 26 male and 18 female, healthy subjects, aged 18-45 years. Each subject received a single dose (100/25 mg) of one of the 2 levodopa/carbidopa formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected just before dosing and 0.17; 0.33; 0.5; 0.67; 0.83; 1.0; 1.25; 1.5; 2.0; 2.5; 3.0; 4.0; 5.0; 6.0; 8.0; 10.0; 12 and 16 hours after administration of the products.

The overall study design and the study population are considered acceptable considering the absorption rate and half-lives. is considered acceptable. The handling of the dropouts is also acceptable.

The study design is acceptable. A GCP statement has been provided.

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
Thirty nine subjects completed the study. Two subjects did not show up for the second treatment, one subject was withdrawn due to positive drug screen test and from two subject who vomited after administration of the products the plasma samples were analysed according the guideline but not included in the pharmacokinetic analysis.

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

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	488 ± 164	502 ± 165	98.4 ± 35.9	3.0 (0.033 – 2.5)	2.06 ± 0.41
Reference	512 ± 198	527 ± 198	107 ± 46.2	2.5 (1.25 – 5.0)	2.07 ± 0.39
***Ratio (90% CI)**	0.97 (0.88 – 1.05)	0.97 (0.89 – 1.05)	0.94 (0.85 – 1.03)	-	-

CV (%)	22.0	21.5	25.0	-	-

$AUC_{0-\infty}$ 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*

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

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1823 ± 533	1859 ± 591	1063 ± 411	1.0 (0.33 – 2.5)	1.71 ± 0.27
Reference	1834 ± 579	1872 ± 578	1040 ± 341	0.83 (0.32 – 2.0)	1.72 ± 0.26
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)	1.00 (0.90 – 1.11)		
CV (%)	7.6%	7.6%	27.7%		

$AUC_{0-\infty}$ 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*

Study II, 250/25 mg formulation

Design

A two-way cross over bioequivalence study was carried out under fasted conditions in 44, 35 male and 9 female, healthy subjects, aged 18-55 years. Each subject received a single dose (250/25 mg) of one of the 2 levodopa/carbidopa formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected just before dosing and 0.17; 0.33; 0.5; 0.67; 0.83; 1.0; 1.25; 1.5; 2.0; 2.5; 3.0; 4.0; 5.0; 6.0; 8.0; 10.0; 12 and 16 hours after administration of the products.

The study population is considered acceptable. The number of dropouts due to vomiting is considered acceptable with this high dose of levodopa and carbidopa. The handling of the dropouts is also acceptable.

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

Twenty nine subjects completed the study. One subject withdrew consent in period 1 and four subjects in period 2. Eight subjects vomited after administration of the products in period 1 and two in period 2 after administration of the test product as well as after the reference product. The plasma samples of the

subjects who vomited were analysed according the guideline but not included in the pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carbidopa under fasted conditions.

Treatment N=29	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	466 ± 138	483 ± 141	90.2 ± 24.3	3.0 (1.0 – 6.0)	2.10 ± 0.30
Reference	456 ± 169	471 ± 171	88.7 ± 38.2	3.0 (1.0 – 6.0)	2.20 ± 0.36
***Ratio (90% CI)**	1.04 (0.96 -1.13)	1.05 (0.96 – 1.13)	1.05 (0.94 – 1.17)	-	-
CV (%)	18.8	18.5	25.1%	-	-

$AUC_{0-\infty}$ 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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levodopa under fasted conditions.

Treatment N=29	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4273 ± 865	4344 ± 866	1730 ± 707	1.25 (0.33 – 4.0)	1.68 ± 0.20
Reference	4295 ± 1032	4370 ± 1028	1846 ± 586	1.50 (0.33 – 3.0)	1.69 ± 0.17
***Ratio (90% CI)**	1.00 (0.96 – 1.04)	1.00 (0.96 – 1.04)	0.92 (0.82 – 1.04)		
CV (%)	8.8%	8.5%	27.1%		

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of of levodopa/carbidopa under fasted conditions, it can be concluded that Levodopa/Carbidopa Mylan 100/25 mg and 250/25 mg tablets and the Sinemet 100/25 mg and 250/25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Levodopa/carbidopa may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of levodopa/carbidopa. Therefore, a food interaction study is not

deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 100/10 mg strength
A biowaiver for the 100/10 mg strength is justified because the following criteria are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

The MEB has been assured that the bioequivalence study has 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
Levodopa/carbidopa was first approved in 1974, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of levodopa/carbidopa 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 Sinemet marketed by Merck Sharp & Dohme.

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. Three tests including the pilot have been performed. A Preliminary Study and a Main Study consisting of two rounds were carried out with 20 participants. As a result of the pilot testing no changes to either the leaflet or the questionnaire were deemed necessary. This is also the case after the first round of testing. After two rounds of user testing, 97.50% of the subjects were able to locate the requested information and gave the correct answer. As a result, no changes were deemed necessary to the patient information leaflet of Levodopa/Carbidopa Mylan.
Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levodopa/Carbidopa Mylan 100/10 mg, 100/25 mg and 250/25 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Sinemet 110, 125 and 275 tablets. Sinemet 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 and are in agreement with other levodopa/carbidopa containing products.

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 Levodopa/Carbidopa Mylan 100/10 mg, 100/25 mg and 250/25 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised> procedure was finished on 24 October 2012. Levodopa/Carbidopa Mylan 100/10 mg, 100/25 mg and 250/25 mg tablets is authorised in the Netherlands on 19 November 2012.

The date for the first renewal will be: 24 October 2017

There were no post-approval commitments made during the procedure.

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
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
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