CBG MEB

Public Assessment Report

Scientific discussion

Levodopa/Carbidopa/Entacapone Mylan 50 mg/12.5 mg/200 mg, Levodopa/Carbidopa/Entacapone Mylan 75 mg/18.75 mg/200 mg, Levodopa/Carbidopa/Entacapone Mylan 100 mg/25 mg/200 mg, Levodopa/Carbidopa/Entacapone Mylan 125 mg/31.25 mg/200 mg, Levodopa/Carbidopa/Entacapone Mylan 150 mg/37.5 mg/200 mg, Levodopa/Carbidopa/Entacapone Mylan 175 mg/43.75 mg/200 mg, Levodopa/Carbidopa/Entacapone Mylan 200 mg/50 mg/200 mg, film-coated tablets

(levodopa/carbidopa/entacapone)

NL/H/3403/001-007/DC

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This module reflects the scientific discussion for the approval of Levodopa/Carbidopa/Entacapone Mylan 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets. The procedure was finalised on 3 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levodopa/Carbidopa/Entacapone Mylan 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets from Mylan B.V.

The product is indicated for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Stalevo 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets (EU/1/03/260/005), which have been centrally registered in the EU by Orion Corporation since 17 October 2003.

The concerned member states (CMS) involved in this procedure were for

- Levodopa/Carbidopa/Entacapone Mylan 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200: Czech Republic, Greece, Spain, France, Ireland, Italy, Slovak Republic and the United Kingdom.
- Levodopa/Carbidopa/Entacapone Mylan 75 mg/18.75 mg/200 mg, 125 mg/31.25 mg/200 mg: Greece, Spain, France, Ireland, Italy and the United Kingdom.
- Levodopa/Carbidopa/Entacapone Mylan 175 mg/43.75 mg/200 mg: France, Ireland, Italy and the United Kingdom.
- Levodopa/Carbidopa/Entacapone Mylan 200 mg/50 mg/200 mg: Czech Republic, Greece, Spain, France, Ireland, Italy and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

- Levodopa/Carbidopa/Entacapone Mylan 50 mg/12.5 mg/200 mg, film-coated tablets is brownish red, round, biconvex and debossed with "50" on one side and plain on the other side. Each tablet contains 50 mg of levodopa, 12.5 mg of carbidopa anhydrous (as 13.5 mg carbidopa monohydrate) and 200 mg of entacapone
- Levodopa/Carbidopa/Entacapone Mylan 75 mg/18.75 mg/200 mg, film-coated tablets is light brownish red, oval, biconvex and debossed with "75" on one side and plain on the other side. Each tablet contains 75 mg of levodopa, 18.75 mg of carbidopa anhydrous (as 20.24 mg carbidopa monohydrate) and 200 mg of entacapone.
- Levodopa/Carbidopa/Entacapone Mylan 100 mg/25 mg/200 mg, film-coated tablets is brownish red, oval, biconvex and debossed with "100" on one side and plain on the other side. Each tablet contains 100 mg of levodopa, 25 mg of carbidopa anhydrous (as 27 mg carbidopa monohydrate) and 200 mg of entacapone.
- Levodopa/Carbidopa/Entacapone Mylan 125 mg/31.25 mg/200 mg, film-coated tablets is light brownish red, oval, biconvex and debossed with "125" on one side and plain on the other side. Each tablet contains 125 mg of levodopa, 31.25 mg of carbidopa anhydrous (as 33.74 mg carbidopa monohydrate) and 200 mg of entacapone.
- Levodopa/Carbidopa/Entacapone Mylan 150 mg/37.5 mg/200 mg, film-coated tablets is brownish red, oval, biconvex and debossed with "150" on one side and plain on the other side. Each tablet contains 150 mg of levodopa, 37.5 mg of carbidopa anhydrous (as 40.48 mg carbidopa monohydrate) and 200 mg of entacapone.

- Levodopa/Carbidopa/Entacapone Mylan 175 mg/43.75 mg/200 mg, film-coated tablets is light brownish red, oval, biconvex and debossed with “175” on one side and plain on the other side. Each tablet contains 175 mg of levodopa, 43.75 mg of carbidopa anhydrous (as 47.23 mg carbidopa monohydrate) and 200 mg of entacapone.
- Levodopa/Carbidopa/Entacapone Mylan 200 mg/50 mg/200 mg, film-coated tablets is dark brownish red, oval, biconvex and debossed with “200” on one side and plain on the other side. Each tablet contains 200 mg of levodopa, 50 mg of carbidopa anhydrous (as 54 mg carbidopa monohydrate) and 200 mg of entacapone.

The film-coated tablets are packed in HDPE bottles with an aluminium induction seal cap and silica gel canister (as a loose component), and aluminium-aluminium blisters.

The excipients are:
Tablet core – croscarmellose sodium (E468), magnesium stearate (E470b), cellulose microcrystalline (E460), poloxamer 188, hydroxypropyl cellulose (E463) and lactose monohydrate.
film-coating – hypromellose Type 2910, titanium dioxide (E171), glycerol (E422), red iron oxide (E172), magnesium stearate (E470b), polysorbate 80 (E433) and hydroxypropyl cellulose (E463).
To create different variations of the tablets, the 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg and 150 mg/37.5 mg/200 mg strengths contain yellow iron oxide (E172).

II.2 Drug Substances

Levodopa
One of the three active substances is levodopa, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Levodopa is a white or almost white, crystalline powder. The active substance is freely soluble in 1 M hydrochloric acid, sparingly soluble in 0.1 M hydrochloric acid, practically insoluble in ethanol (96%) and slightly soluble in water. No polymorphic forms of this molecule are reported in the literature.

The CEP procedure is used for levodopa. 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 Ph.Eur.

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

Quality control of drug substance
The levodopa specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Levodopa is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Carbidopa
The second substance is carbidopa, an established active substance described in the Ph.Eur. Carbidopa is a white or yellowish white powder. The active substance is slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in methylene chloride and it dissolves in dilute solutions of mineral acids. The compound crystallizes as monohydrate. There are no literature reports on polymorphic forms of carbidopa.

The CEP procedure is used for carbidopa. 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 Ph.Eur.

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

Quality control of drug substance
The carbidopa specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional test from the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Entacapone
The third active substance is entacapone, an established active substance described in the Ph.Eur. Entacapone is a greenish yellow or yellow powder. The active substance is practically insoluble in water, soluble or sparingly soluble in acetone and slightly soluble in anhydrous ethanol. Entacapone shows polymorphism, form A is consistently manufactured. Entacapone is not having any chiral carbon in its chemical structure; hence it does not posses any optical isomerism.

The CEP procedure is used for entacapone. 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 Ph.Eur.

The Active Substance Master File (ASMF) procedure is also used for entacapone. 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
Entacapone is manufactured by two manufacturers. For one manufacturer a CEP has been submitted; therefore no details on the manufacturing process have been included. For the second manufacturer the manufacturing process is adequately described. The process consists of two steps. No metal catalysts or Class 1 solvents are used. The proposed starting materials are acceptable.

Quality control of drug substance
The entacapone specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for four production scale batches.

Stability of drug substance
For entacapone, manufactured by manufacturer one, no retest period was claimed on the CEP. Hence, stability data on three batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) have been provided, confirming a retest period of 5 years when stored in the proposed packaging and protected from light.
For the ASMF of entacapone (second manufacturer) stability data on eight batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) have been provided. Based on the results, a retest period of 5 years can be granted, when packed in the proposed packaging in order to protect

the drug substance from light. This is the recommended Ph.Eur. storage condition and no additional photostability studies have been preformed by the ASMF holder.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.

Based on the provided development data, from a chemical pharmaceutical point of view, the test and reference product are considered essentially similar. The composition of the strengths is not quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substances is not the same for all strengths. Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies. Therefore, two bioequivalence studies were performed with the lowest 50 mg/12.5 mg/200 mg and highest 200 mg/50 mg/200 mg strength, representing extremes. Subsequently, appropriate *in vitro* dissolution data have confirmed the adequacy of waiving additional *in vivo* bioequivalence testing.

The MAH has committed to perform comparative dissolution profile testing on the first three production batches versus the test batches used in the bioequivalence trials. The results will be provided at the authority's request or, if the dissolution profiles are not similar, together with proposed action to be taken.

Manufacturing process

The manufacturing process includes wet granulation, followed by drying and milling, preparation of the final tableting mass, compression of the tablet cores and film-coating. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for four pilot scale batches of all strengths in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with the Ph.Eur. monographs. 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 tests for appearance, average tablet weight, water, disintegration, uniformity of mass, identification, assay of active substances, dissolution of drug substances at specific time points, dosage uniformity, related substances, residual solvent, identification and microbial controls. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 4 batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from four pilot scale batches per strength in accordance with applicable European guidelines. The batches were stored at 25°C/60% RH (up to 24 months) and 30°/75% RH (up to 12 months) and 40°C/75% RH (up to 6 months). The batches were stored in the proposed packages. The observed trends remained within specifications. A photostability study demonstrated that the drug product is not sensitive to light.

On basis of the data submitted, a shelf life was granted of 30 months. The following storage conditions are acceptable for when the product is packed in blisters: 'Store below 25°C' and 'Store in the original packaging in order to protect from moisture'. For a bottle packaging, the storage conditions: 'Store below 25°C' and 'Store in the original packaging and keep the bottle tightly closed in order to protect from moisture' are acceptable. After first opening the tablet bottle, a shelf life of three months is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For the production of lactose monohydrate milk sourced from healthy animals in the same conditions as milk collected for human consumption is used. The lactose is prepared without the use of other ruminant materials than calf rennet. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levodopa/Carbidopa/Entacapone Mylan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levodopa/Carbidopa/Entacapone Mylan is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Stalevo which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levodopa, carbidopa and entacapone 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products levodopa/carbidopa/entacapone 50 mg/12.5 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets (PharmaSwiss Ceská republika s.r.o., Czech Republic) are compared with the pharmacokinetic profiles of the reference products Stalevo 50 mg/12.5 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets (Orion Corporation, Finland).

The choice of the reference product in the bioequivalence studies is accepted, as Stalevo has been registered trough a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the additional strengths 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg and 175 mg/43.75 mg/200 mg was applied for.

According to the "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions 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),If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered.
    i. the amount of the active substance(s) is less than 5% of the tablet core weight, the weight of the capsule content
    ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed
    iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths
d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

For the products to be registered, requirements a) and b) are fulfilled. As bioequivalence studies were submitted with the lowest and highest strength the bracketing approach is used and therefore requirement c) is not applicable.

In vitro dissolution data at the required pH 1.2, 4.5 and 6.8 for all three components of the different strengths were submitted. Similarity is shown as all f2 values are above 50. Biowaivers for the additional intermediate strengths can therefore be granted.

Bioequivalence studies

Bioequivalence study I: 50 mg/12.5 mg/200 mg strength

Design

A single-dose, single-centre, randomised, open-label, four-period, laboratory-blind, two-sequence, replicate bioequivalence study was carried out under fasted conditions in 38 healthy male (n=12) and females (n=26) subjects, aged 21-51 years. Each subject received a single dose (10 mg) of domperidone with 240 ml of water approximately 1 hour before the levodopa/carbidopa/entacapone administration in order to provide blockade of the pharmacological effects of levodopa/carbidopa/entacapone. Thereafter, a single dose of the assigned 50 mg/12.5 mg/200 mg levodopa/carbidopa/entacapone formulation was administered in the morning. The tablet was orally administered r after an overnight fast of at least 10 hours. There were 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 6, 8, 10 and 14 hours after administration of the products.

The design of the study is acceptable. The products are immediate release formulations which can be taken with or without food. Hence, studies under fasted conditions are appropriate. The study was performed using a replicate design, which is common for highly variable drug products like Levodopa/Carbidopa/Entacapone film-coated tablets. The intra-subject variability was high (>30%) for the reference product. Therefore, as predefined in the protocol, the replicate design allows the bioequivalence acceptance interval for C_{max}, to be widened to 72.73% - 137.50%.

Because of the known pharmacokinetic profile of Levodopa/Carbidopa/Entacapone Mylan, it was determined that a 7 day washout period between drug administrations would be sufficient,

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
One subject was withdrawn in period 1 due to a gastro-intestinal event, however returned to complete the rest of the study. Therefore, all 38 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	953 ± 242	442 ± 103	1.0 (0.25 – 2.67)
Reference	1017 ± 228	470 ± 125	1.0 (0.5 – 3.38)
***Ratio (90% CI)**	0.94 (0.91 – 0.97)	0.95 (0.90 – 1.00)	--
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			

**ln-transformed values*

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	223 ± 85	49.2 ± 18	2.33 (1.67 – 6.10)
Reference	221 ± 80	48.4 ± 19	2.67 (1.33 – 6.03)
***Ratio (90% CI)**	0.99 (0.92 – 1.07)	1.02 (0.94 – 1.10)	--
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			

**ln-transformed values*

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1522 ± 416	1405 ± 732	1.0 (0.25 – 3.67)
Reference	1542 ± 466	1238 ± 619	0.75 (0.25 – 6.0)
***Ratio (90% CI)**	1.00 (0.97 – 1.04)	1.14 (1.03 – 1.26)	--
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			

**ln-transformed values*

Safety

A total of 17 (45%) subjects reported 48 adverse events (AEs) over the course of the study. The incidence of AEs was similar for subjects dosed with the test product and reference product (20% vs. 16%, respectively). All of the AEs were deemed mild (43/48, 90%) and moderate (5/48, 10%) in severity. No severe AEs were observed during the study.

Bioequivalence study II: 200 mg/50 mg/200 mg strength

Design

A single-dose, single-centre, randomised, open-label, four-period, laboratory-blind, two-sequence, replicate bioequivalence study was carried out under fasted conditions in 40 healthy male (n=29) and females (n=11) subjects, aged 20-55 years. Each subject received a single dose (10 mg) of domperidone with 240 ml of water approximately 1 hour before the levodopa/carbidopa/entacapone administration in order to provide blockade of the pharmacological effects of levodopa/carbidopa/entacapone. Thereafter, a single dose of the assigned 50 mg/12.5 mg/200 mg levodopa/carbidopa/entacapone formulation was administered in the morning. The tablet was orally administered after an overnight fast of at least 10 hours. There were 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 6, 8, 10 and 14 hours after administration of the products.

The design of the study is acceptable. The products are immediate release formulations which can be taken with or without food. Hence, studies under fasted conditions are appropriate. The study was performed using a replicate design, which is common for highly variable drug products like Levodopa/Carbidopa/Entacapone film-coated tablets. The intra-subject variability was high (>30%) for the reference product. Therefore, as predefined in the protocol, the replicate design allows the bioequivalence acceptance interval for C_{max}, to be widened to 70.89% - 141.06%.
Because of the known pharmacokinetic profile of Levodopa/Carbidopa/Entacapone Mylan, it was determined that a 7 day washout period between drug administrations would be sufficient,

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

Three subjects discontinued the study: one for personal reasons (not related to clinical events), one for personal reasons (related to the clinical events) and one for safety reasons. Therefore, a total of 37 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=37	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	5651 ± 1406	1903 ± 532	1.33 (0.75 – 3.67)
Reference	5651 ± 1235	1928 ± 514	1.33 (0.5 – 3.67)
***Ratio (90% CI)**	0.99 (0.97 – 1.02)	0.99 (0.94 – 1.03)	--
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			

**ln-transformed values*

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carbidopa under fasted conditions.

Treatment N=37	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h

Test	1065 ± 346	193 ± 66	3.33 (1.38 – 6.07)
Reference	1065 ± 364	195 ± 67	3.0 (1.67 – 6.00)
***Ratio** **(90% CI)**	1.01 (0.95 – 1.07)	0.99 (0.92 – 1.05)	--
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			

**ln-transformed values*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of entacapone under fasted conditions.

Treatment **N=37**	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1602 ± 480	1378 ± 767	0.75 (0.25 – 3.67)
Reference	1549 ± 422	1276 ± 125	0.75 (0.25 – 4.0)
***Ratio** **(90% CI)**	1.03 (0.99 – 1.06)	1.12 (1.02 – 1.25)	--
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			

**ln-transformed values*

Safety
A total of 27 (68%) subjects reported 91 AEs over the course of the study. The incidence of AEs was similar for subjects dosed with the test and reference product (35% vs. 32%, respectively). Drug-related AEs were also reported with a similar incidence (test 33% vs. reference 28%). Most of the AEs were deemed mild (65/91, 71%) and moderate (25/91, 27%) in severity. No severe adverse events were observed during the study.

Conclusion on bioequivalence studies:
The reference product was found to be highly variable for C_{max} with an intra-subject variability greater than 30%. Widening of the acceptance intervals was allowed but, based on the study results, proved not to be necessary. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Levodopa/Carbidopa/Entacapone Mylan is considered bioequivalent with Stalevo.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Stalevo.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Rhabdomyolysis • Neuroleptic Malignant Syndrome • Liver and biliary system disorders and liver laboratory abnormalities • Impulse control disorders (i.e. pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and binge eating)

	• Depression with suicidal tendencies • Gastrointestinal haemorrhage • Colitis • Thrombocytopenia • Orthostatic hypotension • Myocardial infarction and other ischaemic heart disease
Important potential risks	• Severe skin and severe allergic reactions • Prostate cancer • Medication error
Missing information	• Use in pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Stalevo. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the PL of a product, with the same active substances, which has been compared with the innovator's PL. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levodopa/Carbidopa/Entacapone Mylan 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Stalevo 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/200 mg and 200 mg/50 mg/200 mg, film-coated tablets. Stalevo 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 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/Entacapone Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 December 2015.

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
Safety, Efficacy and Pharmacovigilance changes; Other variation; Update SPC	NL/H/3403/ 1-6/IB/001	IB	29-04-2016	20-09-2016	Non approval	No
Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites)	NL/H/3403/ 1-7/IA/003	IA	14-09-2016	10-10-2016	Approval	No
Change in test procedure for the finished product; Other changes to a test procedure (including replacement or addition)	NL/H/3403/ 1-7/IB/004	IB	27-09-2016	27-10-2016	Approval	No