Type II variation
Public Assessment Report

Sinemet CR 125, modified-release tablets
Sinemet CR 250, modified-release tablets

carbidopa/levodopa

Marketing Authorisation Holder:
Merck Sharp & Dohme B.V.

NL License RVG 13706 and 15175

14 October 2013

I. RECOMMENDATION

Based on the review of the data on quality and pharmacokinetics, the MEB considers that the variation for Sinemet CR 125 and 250, modified-release tablets (carbidopa/levodopa), in the treatment of *idiopathic Parkinson's disease, in particular to shorten the "off" period in patients who have previously been treated with immediate-release levodopa/decarboxylase inhibitors, or with just levodopa who showed motor fluctuations* for the following proposed changes 'change in manufacturing site of the finished product and change in composition' is approvable.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

Sinemet CR has been registered in the Netherlands since 25 July 1990 (250 mg) and 5 August 1991 (125 mg). The product contains the active substances L-dopa (levodopa) and carbidopa and is indicated for the treatment of idiopathic Parkinson's disease. The recommended initial dose is 1 - 4 tablets of the 25 mg/100 mg strength per day or 2 tablets of the 50 mg/200 mg strength per day.

Levodopa is a precursor of dopamine, and is given as replacement therapy in Parkinson's disease.
Carbidopa, which does not cross the blood-brain barrier, inhibits only the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine.

Scope of the variation
A type II variation was applied for in December 2010, which concerns a change in the composition of two strengths of Sinemet CR tablets (carbidopa/levodopa), *i.e.* 25 mg/100 mg and 50 mg/200 mg. This application concerns also a change in manufacturing site. The proposed manufacturing process is identical to the already approved manufacturing process used for production of the US marketed modified-release tablets with minor differences in the compression process.

As the product from the new manufacturing site differs qualitatively and quantitatively in composition from the initial formulations, the MAH submitted additional pharmacokinetic studies in support of the proposed change in formulation. Bioequivalence studies versus the previous formulation have been performed for Sinemet CR 250 (fasted, fed and steady state conditions) and Sinemet CR 125 modified-release tablets (fasted conditions). The results of these four studies are discussed under III.2 'Clinical aspects'.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

Active substances
Carbidopa drug substance used in the manufacture of Sinemet CR meets the requirements of the Ph. Eur. with additional limits as set on the CEP.
For levodopa the Active Substance Master File (ASMF) procedure was used. This drug substance meets the requirements of the Ph. Eur. with additional limits for particle size. After finalisation of this variation procedure, the ASMF for levodopa has been replaced with a CEP. Both active substances are adequately controlled.

Medicinal product
The modified-release tablet formulation for the proposed new production site differs from the previously approved formulation. The differences between the formulations are the controlled release polymer, colorants and make-up of the granulating solution.
The colorants only serve for product definition and have no pharmaceutical function. In addition, the tablet weight differs; the proposed 25/100 mg and 50/200 mg tablets are slightly larger than the original tablet.

Appearance has changed as follows:

Previous	New
25/100 mg Pink-colored, oval, tablet with SINEMET CR on one side and 601 on the other	25/100 mg Dappled purple, oval-shaped tablet, plain on one side and engraved 601 on the other
50/200 mg Peach-colored, oval tablet with SINEMET CR on one site and scored with MSD 521 on the other	50/200 mg Dappled purple, oval-shaped tablet, plain on one side and engraved 521 on the other

Control of the new process and formulation
The development of the formulation is described and the function of the ingredients has been sufficiently explained. The 25/100 mg and 50/200 mg strengths are dose proportional. The manufacturing process includes fluid bed granulation/fluid bed drying followed by milling, lubrication and compression into tablets. The process has been described in sufficient detail and sufficiently validated.
The product specifications are acceptable. The analytical procedures are described and validation data have been presented. Batch analysis data have been provided for both strengths.
The ingredients comply with the Ph.Eur., except for the colorants, for which appropriate specifications have been laid down.

The newly introduced packaging is an HDPE bottle with foil induction seals and PP closure. The former packaging was amber glass bottles and aluminium/aluminium blisters. Sufficient data on the proposed container-closure system were presented.

Stability studies have been initiated on the proposed formulation. Studies were conducted with the 100's count HDPE bottles for each product strength (25/100 mg and 50/200 mg) at both 25ºC/60% RH long term and 40ºC/75% RH accelerated conditions. Up to 12 months data have been submitted. The old formulation has a shelf life of 2.5 years. The MAH proposed a shelf life of 24 months without special storage conditions. In view of the submitted data and the data for the current formulation, the shelf life of 24 months can be granted. The product does not require special storage conditions.
An in-use study is not considered necessary in view of (i) the dosing regime of at least 2 tablets a day, (ii) quantity of 100 tablets per container, and (iii) the stability of the drug substances.

Comparative dissolution
In vitro dissolution data were generated for the formulations utilized in the bioequivalence studies. Comparable dissolution between these formulations and the respective strength of the previously marketed formulation could not be concluded based on dissolution data in three media (pH 1.2, pH 4.5 and pH 6.8), neither could comparable dissolution be demonstrated between the 2 strengths of the proposed composition. However, in view of this variation application the discrepancy of *in vitro* dissolution is considered of minor importance as the *in vivo* bioequivalence is pivotal in the assessment of bioequivalence of these formulations. The bioequivalence results are discussed below.

III.2 Clinical aspects

Pharmacokinetics
As the product from the new manufacturing site differs qualitatively and quantitatively in composition from the initial formulations, the MAH submitted additional pharmacokinetic studies in support of the proposed change in formulation. The following four pharmacokinetic studies were submitted to support the application:

- **Bioequivalence study I -** Single-dose fasting bioequivalence study comparing Sinemet® CR tablets (50 mg/200 mg) (old versus new formulation) in healthy adults
- **Bioequivalence study II -** Single-dose fed bioequivalence study comparing Sinemet® CR tablets (50 mg/200 mg) (old versus new formulation) in healthy adults
- **Bioequivalence study III -** Single-dose fasting bioequivalence study comparing Sinemet® CR tablets (25 mg/100 mg) (old versus new formulation) in healthy adults
- **Bioequivalence study IV -** Steady-state fasting single-dose bioequivalence study comparing Sinemet® CR tablets (50 mg/200 mg) (old versus new formulation) in healthy adults

The studies were open-label, two-treatment, randomized, two-period crossover studies to investigate bioequivalence. The reference product is the Sinemet CR modified-release tablet approved in the Netherlands ('old formulation'). All studies were performed in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and protocols were approved by an ethics committee. The design of these studies, bioanalytical methods and pharmacokinetic and statistical analysis were in accordance with the guidelines in force at the time of application.

Bioequivalence study I - 250 mg, fasting conditions
This was an open-label, two-treatment, single-dose, randomized, two-period crossover study to demonstrate the bioequivalence after administration of Sinemet CR Tablets (50 mg carbidopa/200 mg levodopa) either as the old or new formulation under fasting conditions.

Sixty (40 males and 20 females) non-smoking subjects with a mean age 25.2 ± 8.5 years and BMI 25.7 ± 3.2 were enrolled and included. After a supervised overnight fast of at least 10 hours, each subject received either the test or reference product, according to the cross-over design. A minimum of 1 week wash-out separated each period. Blood samples were taken pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours post study drug administration.

One subject withdrew consent during period I due to adverse events (AE) (headache and nausea), two subjects failed to report to the clinic for Period II, one subject had a positive urine drug screen at check-in for Period II and another subject was discontinued in Period I due to an AE (vomiting). Three more subjects were discontinued in Period II due to vomiting.
Fifty-two (52) subjects completed the clinical study and were analyzed for PK.

Table 1. Pharmacokinetic parameters for carbidopa (n=52, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (NEW formulation)	891 ± 376	911 ± 379	183 ± 85	4.25 (1.5-6.0)
Reference (OLD formulation)	850 ± 321	868 ± 322	166 ± 69	4.5 (1.5-6.0)
***Ratio (90% CI)**	1.03 (0.96-1.11)	1.03 (0.96-1.11)	1.09 (1.00-1.17)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed data*

Table 2. Pharmacokinetic parameters for levodopa (n=52, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (NEW formulation)	4102 ± 1158	4174 ± 1168	1163 ± 438	2.5 (0.8-5.0)
Reference (OLD formulation)	4085 ± 944	4168 ± 957	1192 ± 431	2.5 (0.8-5.0)
***Ratio (90% CI)**	1.00 (0.96-1.03)	0.99 (0.96-1.03)	0.98 (0.90-1.06)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed data*

Bioequivalence study II - 250 mg, fed conditions

This was an open-label, two-treatment, single-dose, randomized, two-period crossover study to demonstrate the bioequivalence after administration of Sinemet CR Tablets (50 mg carbidopa/200 mg levodopa) either as the old or new formulation under fed conditions.
Fifty-four subjects (39 males and 15 females; non-smokers, mean age 24.4 ± 6.4, mean BMI 25.8 ± 3.5) were included.

On study day 1, each subject received either a single oral dose of 50 mg/200 mg of the test product (new formulation), or of the reference product (old formulation). Dosing occurred 30 minutes after the initiation of an FDA standard, high fat breakfast (protein: 150 calories, carbohydrates: 250 calories and fat: 500-600 calories) preceded by an overnight fast of at least 10 hours. Following a 7 day washout period, all subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization.

In each study period, blood samples were collected within 120 minutes prior to dose administration (0 hour) and post-dose at study hours 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, 16 and 24.

Fifty-one (51) subjects completed the clinical study. Two subjects withdrew consent due to personal reasons and one subject withdrew during Period I due to AEs (nausea, vomiting, and dizziness). These subjects were not included in the analysis.

Table 3. Pharmacokinetic parameters for carbidopa (n=51, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$** ng/ml/h	C_{max} ng/ml	t_{max} h
Test (NEW formulation)	515 ± 157	531 ± 157	100 ± 33	4.5 (1.5-8.0)
Reference (OLD formulation)	497 ± 136	521 ± 135	99 ± 31	4.0 (2.5-12.0)
***Ratio (90% CI)**	1.02 (0.95-1.09)	1.00 (0.94-1.07)	1.01 (0.94-1.08)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed data, **n=49*

Table 4. Pharmacokinetic parameters for levodopa (n=51, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (NEW formulation)	4354 ± 939	4439 ± 943	1248 ± 393	3.0 (1.0-6.0)
Reference (OLD formulation)	4240 ± 786	4334 ± 788**	1264 ± 438	3.0 (1.0-8.0)
***Ratio (90% CI)**	1.02 (0.98-1.05)	1.01 (0.98-1.05)	1.00 (0.91-1.10)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed data, **n=50*

Bioequivalence study III - 125 mg, fasting conditions
This was an open-label, two-treatment, single-dose, randomized, two-period crossover study to demonstrate the bioequivalence after administration of Sinemet CR Tablets (25 mg carbidopa/100 mg levodopa) either as the old or new formulation under fasting conditions.

Fifty-six (30 males and 26 females) non-smoking subjects with a mean age 25.6 ± 8.5 years and BMI 25.4 ± 3 were included. After a supervised overnight fast of at least 10 hours, each subject received either the test or reference product, according to the cross-over design. A minimum of 1 week wash-out separated each period. Blood samples were taken pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours post study drug administration.

Two subjects withdrew consent prior to Period II dosing, one subject was discontinued in Period I due to an AE (vomiting) and another subject was discontinued prior to Period II dosing due to consumption of hydrocodone during the washout period to treat an AE (migraine). Fifty-two (52) subjects completed the clinical study and fifty-four (54) subjects were analyzed.

Table 5. Pharmacokinetic parameters for carbidopa (n=52, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (NEW formulation)	427 ± 185	442 ± 188	98 ± 42	3.75 (1.5-5.0)
Reference (OLD formulation)	508 ± 202	522 ± 203	112 ± 40	3.5 (1.5-5.0)
***Ratio (90% CI)**	0.84 (0.78-0.90)	0.84 (0.78-0.90)	0.86 (0.797-0.937)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed data*

Table 6. Pharmacokinetic parameters for levodopa (n=52, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (NEW formulation)	2036 ± 540	2073 ± 542	694 ± 188	2.0 (0.5-4.5)
Reference (OLD formulation)	2087 ± 518	2123 ± 518	871 ± 292	1.75 (0.5-4.0)
***Ratio (90% CI)**	97.57 (0.94-1.02)	0.98 (0.94-1.02)	0.81 (0.76-0.87)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed data*

Bioequivalence study IV - 250 mg, steady-state, fasting conditions

This was an open-label, two-treatment, randomized, two-period, multiple-dose (ten doses per period), crossover study to demonstrate bioequivalence after attainment of steady-state conditions of the fixed dose combination of Sinemet 50 mg/200 mg, modified-release tablets, either as the old or new formulation, following administration of a single, oral dose of 50 mg/ 200 mg (1 x 50 mg/ 200 mg) tablets administered three (3) times a day for three (3) days and administered one (1) time on day four (4) for a total of ten (10) doses under fasting, steady-state conditions.

Fifty-four (54) subjects (36 males and 18 females) non-smoking subjects with a mean age 28 ± 9.5 years and BMI 26.7 ± 3.9 were enrolled and included.
Subjects were housed from at least 14 hours prior to dosing until 12 hours after the last dosing (Dose 10 on Day 4) of each period. Following an overnight fast of at least 10 hours, the study drug was administered every 8 hours for a total of 10 doses per period. A fast was maintained for at least 4 hours after dosing only with the 1st and 10th dose administration of each period. A minimum 7-day washout separated the last dose of Period I and the first dose of Period II. Blood samples were

collected within 10 minutes prior to dose administration (0 hour) on Day 1, pre-dose of the 8th and 9th dose (Day 3), and then pre-dose (Day 4) and after dose administration at study hours 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8.

Forty-six (46) subjects completed the clinical study but only 45 subjects were included in the analysis. The following subjects were not included in the statistical analysis:

- Two subjects were discontinued due to adverse events.
- Two subjects withdrew consent.
- One subject was discontinued for a positive drug screen on Period II check in.
- Two subjects were discontinued due to a failure to comply with protocol requirements during Period II (positive nicotine test results).
- One subject was discontinued due to the wrong treatment being administered on Dose 10 of Period I.
- One subject completed the study but was discontinued due to protocol violation.

Table 7. Pharmacokinetic parameters for carbidopa in steady-state (n=45, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-T} ng/ml/h	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	$t_{max,ss}$ h
Test (NEW formulation)	981 ± 297	210 ± 71	45 ± 20	4.5 (2.0-6.0)
Reference (OLD formulation)	1032 ± 355	213 ± 77	44 ± 17	4.5 (1.5-6.0)
***Ratio (90% CI)**	0.96 (0.90-1.03)	0.99 (0.91-1.07)	1.00 (0.90-1.13)	--

AUC_{0-T} Area under the plasma concentration curve during a dosage interval at steady state
$C_{max,ss}$ Maximum plasma concentration at steady state
$C_{min,ss}$ Minimum plasma concentration at steady state
$t_{max,ss}$ Time until Cmax,ss is reached

**ln-transformed values*

Table 8. Pharmacokinetic parameters for levodopa in steady-state (n=45, non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-T} ng/ml/h	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	$t_{max,ss}$ h
Test (NEW formulation)	4473 ± 1111	1290 ± 369	106 ± 43	2.0 (0.5-4.0)
Reference (OLD formulation)	4682 ± 1332	1405 ± 430	99 ± 41	1.5 (0.5-4.0)
***Ratio (90% CI)**	0.96 (0.93-1.00)	0.92 (0.87-0.98)	1.06 (0.98-1.16)	--

AUC_{0-T} Area under the plasma concentration curve during a dosage interval at steady state
$C_{max,ss}$ Maximum plasma concentration at steady state
$C_{min,ss}$ Minimum plasma concentration at steady state
$t_{max,ss}$ Time until Cmax,ss is reached

**ln-transformed values*

Discussion on the pharmacokinetic results

Pharmacokinetic studies were performed in accordance to the guidelines in force at the time of submission. For the higher strength (50 mg/200 mg), the mean ratios of the different pharmacokinetic parameters between the current product and the previous product in the fasted state (study I), fed state (study II) and under steady state (study IV) were within bioequivalence acceptance criteria of 80% - 125%.

In the fed study, the AUC_{0-t}, AUC_{inf} and C_{max} of carbidopa of the test and reference product were reduced by 41% to 45% and increased in levodopa by 4% to 7% in comparison with the fasted state.

The MAH has convincingly argued that although the fed state led to a considerable decrease in carbidopa levels, there is still a sufficient amount of carbidopa to block peripheral aromatic amino acid

decarboxylase activity and thus ensuring clinically effective levels of levodopa in the brain. Hence, in line with the current SPC, it is agreed that information of the effects of a fed state on carbidopa and levodopa need not be reflected in the SPC.
As the 50 mg/200 mg strength of the proposed product was shown to be bioequivalent to the current innovator 50 mg/200 mg formulation, the benefit/risk of the two products is considered to be similar.

Bioequivalence for the old and new formulations of the lower strength (25 mg/100 mg) under fasted conditions was not demonstrated in accordance with bioequivalence criteria. In the single-dose fasting study (study III) for carbidopa the AUC_{0-t}, AUC_{inf} and C_{max} were not bioequivalent and for levodopa the confidence interval for the C_{max} exceeded the lower bioequivalence acceptance criterion of 80%. Thus, bioequivalence between the proposed product and the current innovator formulation could not be demonstrated for the lower strength 25 mg/100 mg. However, this has no clinically relevant impact on efficacy and the benefit/risk of the two formulations is considered to be similar. The deviation for the carbidopa parameters AUC_{0-t}, AUC_{inf} and C_{max} is not considered an issue as carbidopa is not the directly relevant drug substance for efficacy. The purpose of carbidopa is to inhibit the extracerebral decarboxylation of levodopa and therefore equivalent presence of levodopa is deemed sufficient to accept the inequivalent concentration of carbidopa. Moreover, the amounts of 50 to 75 mg/day carbidopa are reported in the literature to achieve adequate peripheral decarboxylase inhibition. In addition, it is noted that the 25/100 mg strength is designed to be used in patients not previously treated with levodopa or for titration purpose in patients who should have the 50/200 mg strength. Taken all together, the reduced carbidopa levels can be considered not to have a clinically relevant impact on efficacy.

The reduced C_{max} of levodopa is not considered an issue as C_{max} is only reduced by a minor extent. From a clinical perspective the lower peak plasma levodopa levels are more indicative for dose related adverse events and C_{min} levels are important for the efficacy of levodopa. Therefore, the benefit/risk of the two formulations is considered to be similar.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The manufacturing site replacement and new formulation for Sinemet CR 125 and 250 are considered approvable from a chemical-pharmaceutical point of view. The manufacturing process is sufficiently validated and the specifications are appropriate. Data on stability, excipients and packaging are satisfactory.

From a pharmacokinetic/pharmacodynamic point of view the change in the composition and manufacturing site can be approved. Bioequivalence has been sufficiently demonstrated for the 50/200 mg tablets. The Board discussed the proposed variation on 2 March 2011 and 13 July 2011. It was concluded that discrepancies observed for the 25/100 mg strength are not considered to have a clinically relevant impact on efficacy and the benefit/risk.
This variation application was approved on 22 December 2011.

V. CHANGES IN PRODUCT INFORMATION

The following SPC sections have been revised: 3 (appearance), 6.1 (excipients), 6.3 (shelf life), 6.4 (storage conditions), 6.5 (package). The PL and labeling have been adapted accordingly.