LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lecigon
(entacapone, carbidopa (monohydrate), levodopa)

SE/H/1986/01/E/01

This module reflects the scientific discussion for the approval of Lecigon. The procedure was finalised on 2018-10-04. For information on changes after this date please refer to the module 'Update'.

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Innehåll

I. INTRODUCTION

Lobsor Pharmaceuticals AB has applied for a marketing authorisation for Lecigon, Intestinal gel, levodopa 20 mg/ml, carbidopa (monohydrate) 5 mg/ml, entacapone 20 mg/ml. The active substance is entacapone, carbidopa (monohydrate), levodopa

Patients with advanced Parkinson´s disease (PD) have several motor- and non-motor complications, which dramatically impair their quality of life (QoL). As the disease progresses, the action of oral treatment with dopamine precursors will gradually shorten.
In advanced PD a short duration of motor response is observed, and "on" time (when anti-parkinson medication provides expected motor effects) is associated with dyskinesia. The "on-off" fluctuations (when anti-parkinson medication does not provide expected motor effects) become unpredictable and the motor fluctuations occur independently of dosing. The principle behind continuous levodopa administration is to deliver an optimised dose that can be kept stable within the patient's individual therapeutic window.
Intra-duodenal/jejunal administration of Levodopa-carbidopa monohydrate (LC) has been shown to result in less variability in plasma concentrations. The reduced fluctuations in plasma concentrations correlate with decreased fluctuations in treatment response. In addition, more stable levodopa plasma concentrations have been observed after the combination of oral levodopa-DDCI with COMT inhibitors.
For approved indication, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

PIP –Paediatric Investigation Plan
The PDCO/EMA has issued a Class waiver for paediatric population for *Lecigon* in the treatment of Parkinson's disease (non-juvenile).

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The non-clinical dossier is entirely bibliographical and no non-clinical studies have been performed with Lecigon or its active components levodopa, carbidopa and entacapone.

III.2 Pharmacology

Lecigon is a triple combination of levodopa, carbidopa and entacapone for continuous intestinal administration. Based on preclinical evidence, the addition of entacapone to levodopa/carbidopa may 1) increase and prolong the systemic exposure to levodopa, 2) increase the uptake of levodopa, and thereby the availability of dopamine, in the brain, 3) decrease the generation of 3-OMD, which in animal models and *in vitro* systems (albeit at high doses/concentrations) is implicated in impaired locomotor activity and neuronal cytotoxicity.

The Applicant has provided adequate information on the pharmacological properties of Lecigon. Conventional safety pharmacology studies have not been performed. This is acceptable, considering the long clinical experience of levodopa/carbidopa for both oral administration (Sinemet) and intestinal infusion (Duodopa), and the combination of levodopa/carbidopa with entacapone for oral administration (Stalevo).

III.3 Pharmacokinetics

No non-clinical pharmacokinetic studies have been performed with Lecigon or its active components levodopa, carbidopa and entacapone. Based on published and publically available data, pharmacokinetic properties of levodopa, carbidopa and entacapone are relatively similar across species, including man, supporting the relevance of animal studies in the evaluation of pharmacology and toxicology.

Oral (and intestinal) bioavailability of levodopa is low, mainly due to extensive metabolism. Carbidopa is routinely added to levodopa treatment to inhibit peripheral decarboxylation and thereby ensure better delivery of dopamine to the regions of interest in the brains of Parkinson's disease patients. As carbidopa is added, the COMT pathway becomes important for elimination of levodopa. Thus, the COMT-inhibitor entacapone is added to the treatment. Entacapone may also lead to better uptake of levodopa in the brain, as the COMT-generated levodopa metabolite 3-OMD competes for transporters over the blood-brain-barrier.

The available animal data supports intestinal delivery as a means to decrease variability in plasma levels of levodopa. Although no studies of intestinally delivered entacapone have been located, it is conceivable that adding entacapone to a continuous intestinal delivery of levodopa/carbidopa may lead to increased exposure to levodopa in relation to dose, and thereby allow for dose-adjustments towards lower levodopa and carbidopa doses.

Since there is extensive clinical experience of the pharmacokinetics of all three components in Lecigon, including their combinations, the pharmacokinetic profiles in animals are of less interest for the overall assessment of the clinical utility of Lecigon.

III.4 Toxicology

The Applicant has provided relevant published literature on toxicology of the active components of Lecigon.

The toxicity observed when studying the combination of carbidopa and levodopa is mainly displayed as clinical signs and largely attributed to exaggerated dopaminergic pharmacology. No distinct organ toxicity has been observed in chronic toxicity studies with entacapone.

Limited amount of *in vitro* mutagenicity information for levodopa and carbidopa, studied separately, has been published. Levodopa/carbidopa has been tested in combination with entacapone in Ames test *in vitro* and a mouse micronucleus test *in vivo* with negative results. Entacapone was found to be genotoxic in two mammalian test systems *in vitro*, suggestive of chromosome type damage. However, the *in vitro* signal of chromosomal damage was not confirmed in two separate tests *in vivo.*

There was no alteration to the tumour profile associated with the administration of levodopa in combination with carbidopa in 2-year carcinogenicity studies in rats. In rat carcinogenicity studies with entacapone, an increased incidence of renal tubular adenomas and carcinomas was noted in males at doses of 400 mg/kg/day were considered likely related to α2-microglobulin deposition. Alteration in the renal handling of this male rat-specific protein is an established mechanism of renal tumorigenesis, and is not considered relevant to humans. In mouse carcinogenicity studies, no treatment-related tumours were observed, but due to high mortality in animals receiving the highest dose of entacapone, the carcinogenic potential of entacapone is not considered fully evaluated.

Available information on reproductive and developmental toxicity identifies a clear risk of embryofoetal toxicity, if used in pregnancy, for combinations of levodopa, carbidopa and entacapone. This risk is largely attributed to effects of levodopa. Levodopa alone, and in combination with carbidopa, has caused visceral and skeletal malformations in rabbits. Consequently, Lecigon should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus.

Impurities

Lecigon contains hydrazine, a known degradation product of carbidopa that can be genotoxic and carcinogenic in animals. The average recommended daily dose of Lecigon is 50 ml (corresponding to 1,75 mg hydrazin/day) and the maximum recommended daily dose is 100 ml (corresponding to 3,5 mg hydrazin/day). The clinical significance of this hydrazine exposure is not known. A warning regarding hydrazine is included in section 4.4 of the SmPC and the non-clinical characteristics of hydrazine are included in section 5.3.

In summary, although no specific toxicology studies have been performed for Lecigon, the safety of the composition and suggested use is considered covered by publically available data together with extensive and long experience of levodopa/carbidopa and levodopa/carbidopa/entacapone products in clinical practice in Parkinson's disease.

III.5 Ecotoxicity/environmental risk assessment

Considering the clinical practice for treating Parkinson's disease patients, it is agreed that the approval of Lecigon is not considered to significantly increase the environmental exposure of levodopa, carbidopa or entacapone, and therefore, an ERA was not requested.

IV. CLINICAL ASPECTS

IV.1 Introduction

Patients with advanced Parkinson´s disease (PD) have several motor- and non-motor complications, which dramatically impair their quality of life (QoL). As the disease progresses, the brain loses the ability to store or use its reserves of dopamine precursors. Therefore, the action of oral treatment with dopamine precursors will gradually shorten. The rapid changes in the motor states between "on" (when anti-parkinson medication provides expected motor effects) and "off" (when anti-parkinson medication does not provide expected motor effects) are called "on-off" fluctuations. In advanced PD, the therapeutic window has narrowed, a short duration of motor response is observed, and "on" time is associated with dyskinesia. The "on-off" fluctuations become unpredictable, i.e. the relationship between doses of anti-parkinson drug taken and the treatment response is lost, and the motor fluctuations occur independently of dosing. Since the fluctuations mirror the levodopa plasma concentrations, continuous drug delivery to enable a steady levodopa plasma concentration is crucial in the treatment of motor symptom fluctuations in advanced PD. The principle behind continuous levodopa administration is to circumvent gastric emptying and deliver an optimised dose that can be kept stable within the patient's individual therapeutic window.
Intra-duodenal/jejunal administration of LC has been shown to result in less variability in levodopa and carbidopa plasma concentrations, which correlate with decreased fluctuations in treatment response. Levodopa-carbidopa monohydrate combination as an intestinal gel (Levodopa-carbidopa intestinal gel; LCIG; Duodopa) granted orphan drug designation in 2001 and has been on the market since 2004-2005, i.e. for more than 10 years.
Oral triple combinations of LCE (Stalevo) have been on the market since 2003. The main PK effect of adding a COMT inhibitor, such as entacapone, to the LC treatment is an extension of levodopa's t½ of approx. 30- 60 min and an increase in bioavailability of 20-40%.

This application is a mixed marketing authorisation application (Art. 8(3) Directive 2001/83/EC) based on the results of the one applicant-sponsored clinical pharmacokinetic (PK) study (LSM-003) with the new triple combination intestinal gel, Lecigon, combined with literature data on oral LCE, i.e. the same 3 substances as in Lecigon, and the intestinal gel with two of the substances (LC) in the same formulation.
A literature search was performed by the applicant to identify published data of relevance for Lecigon. The rationales for the selection of the supportive studies with regard to PK, efficacy and safety, respectively, were the following:

PK:
- The applicant-sponsored LSM-003 study is the only (PK-) study conducted with Lecigon.
- The published 'DuoCOMT' study (1) is the only identified published (PK-) study with LCIG and oral entacapone.

Efficacy and safety of LCIG:
- The study published by Olanow et al. (2) is the only double-blind study with LCIG (a comparison of LCIG and oral immediate-release [IR] LC).
- The study published by Slevin et al. (3) is a long-term (52 weeks) open-label extension of the above-mentioned supportive double-blind study published by Olanow et al. (2).
- The prospective, open-label, long-term (54 weeks) study published by Fernandez et al. (4) is the largest (n=354) study with LCIG.

Efficacy of oral LCE:
- The 'SEESAW' study published by the Parkinson Study Group (5) was the only identified study, which enrolled patients with advanced PD, i.e. with motor fluctuations, and in which the active substances were LCE (e.g. studies with unspecified DDCI instead of carbidopa did not qualify), and which included a direct comparison of oral LCE vs. oral LC of otherwise identical formulations.

Safety of oral LCE:

The following 3 studies were the only identified studies which enrolled patients with advanced PD, i.e. with motor fluctuations, and in which the active substances of any oral formulation in one study treatment arm were LCE (e.g. studies with unspecified DDCI instead of carbidopa did not qualify).

- The placebo-controlled, double-blind 'SEESAW' study published by the Parkinson Study Group (5) comparing oral LCE with oral LC.
- The randomised, prospective, open-label, parallel-group 'TC-INIT' study published by Brooks et al. (6) comparing a fixed oral combination of LCE (Stalevo) with oral IR LC plus adjunct entacapone.
- The randomised, double-blind, double-dummy, cross-over 'CLE with OLE' study published by Stocchi et al. (7) comparing IR LC plus entacapone with extended-release (ER) LC.

Supportive clinical studies in this application

Study	**Study description**	**Treatment duration**	**No. of patients**
PK studies with LECIGON or LCIG plus oral entacapone			
LSM-003 NCT02448914	A 2-period, open label, randomised, cross-over study comparing LECIGON with LCIG.	14 h	Treated and completed: 11
DuoCOMT Nyholm 2012 (1) NCT00906828	A 3-period, single-blinded, randomised, cross-over study investigating whether the levodopa dose can be reduced by 20% when oral COMT inhibitor is added.	8 h	Treated: 10 Completed: 9
Studies supporting efficacy and safety of LCIG			
Olanow 2014 (2) NCT00357994/ NCT00660387	A prospective, randomised, placebo-controlled, parallel group, double-blind, double-dummy, double-titration study comparing LCIG with oral IR LC.	12 weeks	Treated: Duodopa: 37 Oral IR LC: 34 Completed: Duodopa: 35 Oral IR LC: 31
Slevin 2015 (3) NCT00360568	A prospective, open-label extension study of the double-blind study published by Olanow et al. in 2014 (2) evaluating long-term safety and efficacy of LCIG.	52 weeks	Entered extension study: 62 Completed: 55
Fernandez 2015 (4) NCT00335153	A prospective, open-label study investigating safety and efficacy of long-term treatment with LCIG.	54 weeks	Enrolled: 354 Completed study: 272
Studies supporting efficacy and safety with oral LCE			
SEESAW Parkinson Study Group 1997 (5)	A placebo-controlled, double-blind, parallel-group, multi-centre study comparing oral LCE with oral LC.	LC: 24 weeks LCE: 24 or 26 weeks	Enrolled: 205 LCE: 103 LC: 102 Completed study (LCE): 90 Completed study (LC): 92
TC-INIT Brooks 2005 (6)	A randomised open-label, parallel-group, study comparing a fixed oral combination of LCE (Stalevo) with oral IR LC plus adjunct entacapone.	6 weeks	Randomised: 177 Stalevo: 83 IR LC + adjunct entacapone: 94 Completed: Stalevo: 77 IR LC + adjunct entacapone: 88
CLE with OLE Stocchi 2014 (7) NCT01130493	A randomised, active-controlled double-blind, double-dummy, cross-over study comparing oral immediate-release (IR) LC plus entacapone with extended-release (ER) LC.	2 + 2 weeks	Enrolled: 110 Randomised: 91 Completed study: 84

These studies are supportive of safety of oral LCE since the patients in one study arm received oral LCE, regardless of formulation (studies supportive of safety had to include patients with advanced PD, i.e. with motor fluctuations, and the active substances had to be LCE, studies with e.g. unspecified DDCI did not qualify). These studies are not supportive with regard to efficacy of oral LCE since they do not include a direct comparison of oral LCE vs. oral LC of otherwise identical formulations; in the "TC-INIT study"(6) patients in both study arms received entacapone and in the "CLE with OLE" study (7), oral IR LCE was compared with oral ER LC (different formulations).

IV.2 Pharmacokinetics

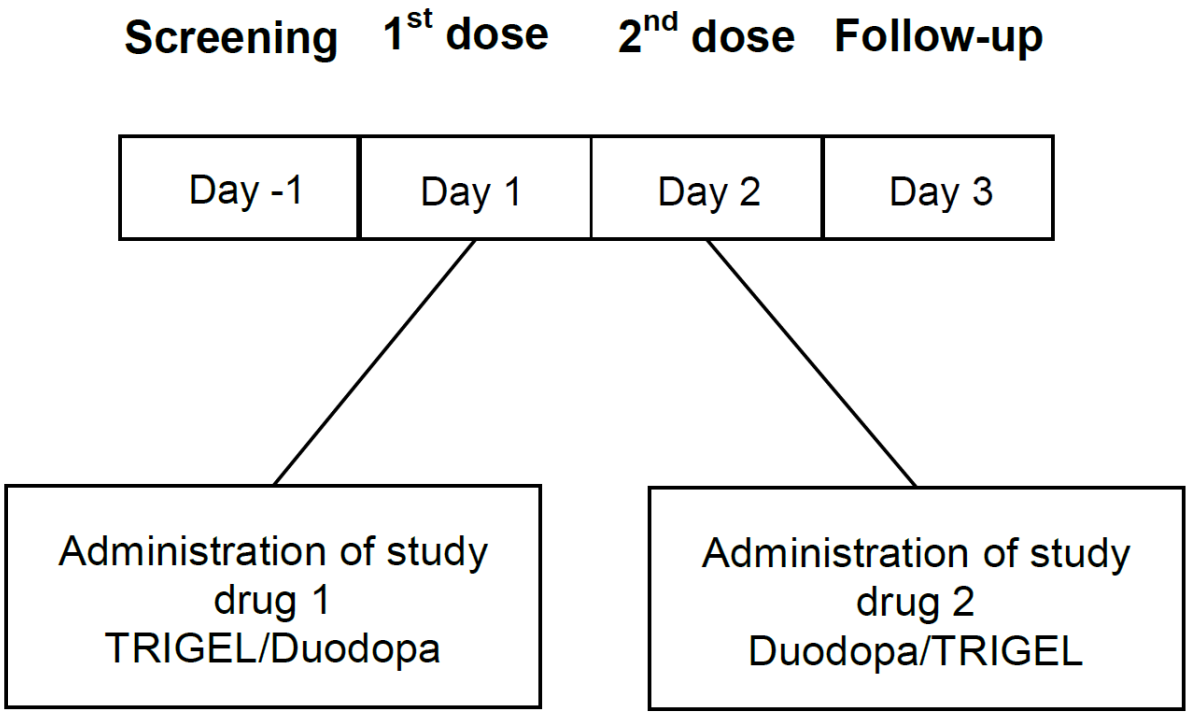
Lecigon is a combination of levodopa, carbidopa, and entacapone. Of the three components, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone modify the peripheral metabolism of levodopa and the half-life of levodopa is prolonged.

The application is mainly based on bibliographic data except for a relative bioavailability study, LSM-003.

Study LSM-003

This was a single centre, two-period, open label, randomised, cross-over study to assess plasma levodopa, carbidopa and entacapone concentrations after continuous infusion of LECIGON (levodopa [20 mg/mL], carbidopa monohydrate [5 mg/mL], and entacapone [20 mg/mL]) or Duodopa (levodopa [20 mg/mL] and carbidopa monohydrate [5 mg/mL]) in patients with advanced Parkinson´s disease

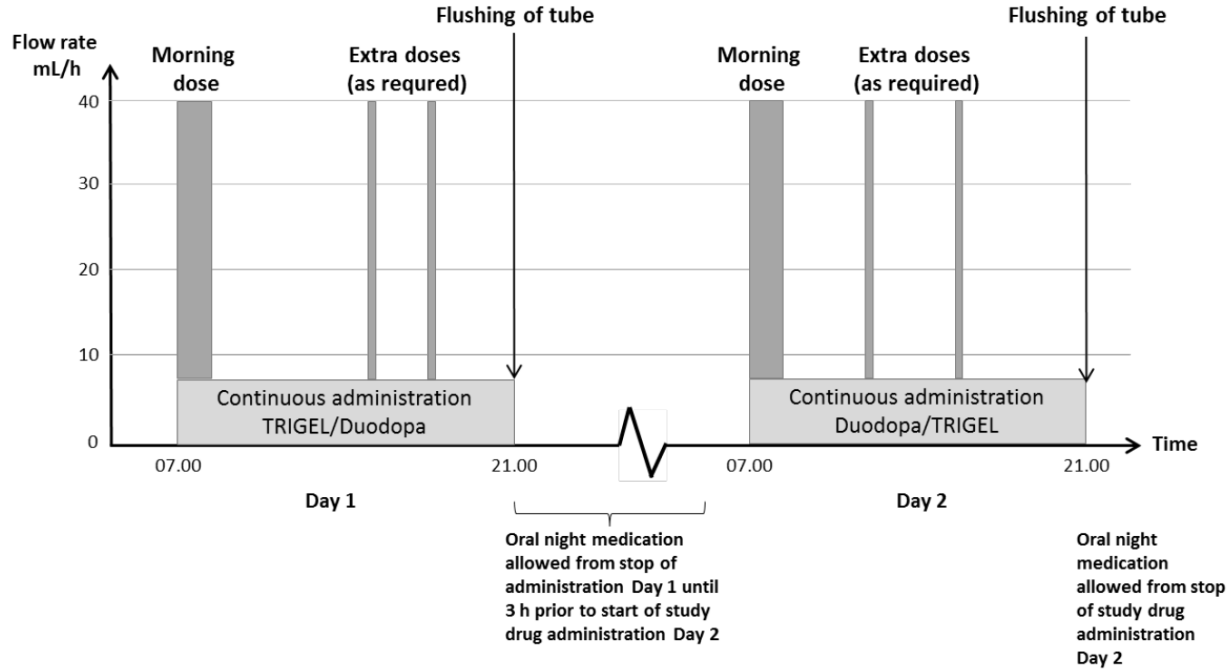
Overall Study Design



All patients received LECIGON (levodopa [20 mg/mL], carbidopa monohydrate [5 mg/mL], and entacapone [20 mg/mL]) and Duodopa (levodopa [20 mg/mL] and carbidopa monohydrate [5 mg/mL]) at two consecutive days.

Each treatment consisted of a morning dose, a continuous administration, extra doses as needed and flushing of the tube at the end of administration. After stop of intestinal administration oral night medication was given as needed, see figure below:

Treatment Sequence



The duration of the continuous administration including the morning dose was 14 h for all patients. Patients were randomised to treatment sequence.

Based on simulations, a LECIGON dose corresponding to 80% levodopa of the optimised Duodopa dose before the study was chosen for the first cohort. The dose reductions for the morning and extra doses were obtained by using an 80% duration and the same flow rates as for Duodopa administration. The dose reduction during continuous administration was achieved by using an 80% flow rate as compared with the flow rate used for continuous Duodopa administration. The interim analysis of the first cohort of five patients showed that 4 out of 5 patients had a slower onset in the morning and were in “OFF” state for a longer period when given LECIGON compared to Duodopa. Therefore, it was decided to increase the morning dose to 90% of the corresponding optimised Duodopa dose in the second cohort.

Apart from the study drug administrations, only oral rescue treatment of PD using Sinemet was allowed during the nights between Day 1, Day 2.

The duration of the continuous administration was set to 14 h for all patients independently of their pre-study Duodopa continuous administration duration.

Sample size

A blinded sample size recalculation based on the first cohort of 5 patients was also made before initiation of inclusion of patients to the second cohort. Based on this interim analysis the second cohort was set to 7 patients. However, only 6 patients were included in the second cohort due to limited capacity at the study site, which meant that inclusion of the 7th patient would delay the study considerably, and the sponsor decided to end the study as the interim analysis had showed a sufficient statistical power even with 11 included patients in total.

NUMBER OF PATIENTS (planned and analysed):

	TRIGEL	Duodopa	Total
No. initially planned:			15
No. planned after sample size recalculation:			12
No. screened:			12
No. randomised and treated:	11	11	11
Males/females:	7/4	7/4	
Mean age (range):	69.5 (63-76)	69.5 (63-76)	
No. analysed for pharmacokinetics:	11	11	11
No. analysed for safety:	11	11	11
No. completed the study:	11	11	11

Sampling
Blood samples were drawn to determine baseline plasma levels in the morning on Day 1. Administration of study drug 1 was initiated and blood sampling was done at pre-specified time points. Administration of study drug 2 started the following day (Day 2), 24 h after start of administration of study drug 1. Blood sampling continued at pre-specified time points. The patients remained at the clinic until a 24 h sample after initiation of the second administration had been taken at the follow-up visit (Day 3).

Levodopa, and its metabolite 3-OMD, carbidopa and entacapone were analysed in the plasma samples by a validated LC-MS/MS assay, and the lower limit of quantification (LLOQ) of the assay were 100 ng/mL, 50 ng/mL, 600 ng/mL and 20 ng/mL for Levodopa, Carbidopa, 3-OMD and entacapone, respectively.

Pharmacokinetic Variables
Pharmacokinetic parameters were derived based on individual plasma concentration versus time data (actual time-points) using a non-compartmental analysis (NCA) in Phoenix WinNonlin® version 6.3, build 6.3.0.395 (Pharsight®, St. Louis, Missouri, USA).

Primary Pharmacokinetic Variable
The primary PK variable was the dose-adjusted area under the plasma concentration-time curve (AUC0-14h/dose) for levodopa during administration (time span 0 to 14 h) of LECIGON and Duodopa.

Secondary Pharmacokinetic Variables
Secondary PK variables were the following:

Intra-CV (3-14 h): Coefficient of variation (CV)=100*sqrt (exp (SDlog*SDlog)-1) where SDlog denotes the standard deviation computed on logged plasma concentrations.

The individual patient´s CV of levodopa plasma concentration during administration of LECIGON and Duodopa, respectively, between 3 and 14 h after start of study drug administration.

AUC0-14h/dose: Dose-adjusted area under the plasma concentration-time curve for carbidopa and 3-OMD during administration (time span 0 to 14 h).

Additional exploratory variables were the following:

- Proportion of patients in need of extra doses per treatment, time points and size of extra doses of LECIGON and Duodopa, and total dose of LECIGON and Duodopa administered during 14 h administration
- Time between stop of study drug administration and administration of night medication
- Characterisation of ON/OFF effect during 14 h administration of LECIGON and Duodopa

Statistical methods
Primary Pharmacokinetic Analysis
The primary endpoint, levodopa AUC0-14h/dose, was derived using the trapezoidal method and divided by the total administered dose of levodopa during the corresponding time interval. The primary endpoint was log transformed and analysed using an ANCOVA, adjusting for treatment, period and patient. The back-transformed ratio of LECIGON over Duodopa was calculated together with 95% confidence intervals (CI) and the associated (2-sided) p-value.

Analysis was first to attempt to show non-inferiority. To show non-inferiority of LECIGON over Duodopa, the lower limit of the two-sided CI for the treatment ratio had to be above the chosen non-inferiority margin of 0.9. If non-inferiority was shown, analysis continued with test of superiority. To show superiority of LECIGON versus Duodopa, the lower confidence limit had to be above 1 (corresponding to a p-value less than 0.05).

Results

The results are presented below.

Summary of levodopa, carbidopa and entacapone PK parameters in study LSM-003

Parameter	TRIGEL		Duodopa		Treatment ratio/difference (95% CI)	p-value[c]
	N	LSMean [a,b]	N	LSMean [a,b]		
Levodopa treatment ratio (TRIGEL/Duodopa)						
AUC_{0-14h}/dose (h*ng/mL/mg) [d]	11	40.6	11	29.4	1.382 (1.264 ; 1.511)	<.0001
AUC_{0-14h} (h*ng/mL)	11	33700	11	32000	1.053 (0.947 ; 1.171)	
AUC_{0-24h}/dose (h*ng/mL/mg) [d]	11	55.0	11	35.8	1.536 (1.406 ; 1.679)	
AUC_{0-24h} (h*ng/mL)	11	45600	11	39000	1.171 (1.052 ; 1.302)	
$AUC_{0.5-3h}$ (h*ng/mL)	11	4060	11	5110	0.794 (0.667 ; 0.945)	
AUC_{14-17h} (h*ng/mL)	11	7800	11	5120	1.524 (1.372 ; 1.692)	
AUC_{last}/dose (h*ng/mL/mg) [d,e]	11	49.4	11	33.9	1.458 (1.343 ; 1.583)	
AUC_{last} (h*ng/mL) [e]	11	41000	11	36900	1.111 (1.006 ; 1.226)	
CV 3-14h (%)	11	13.8	11	10.6	1.296 (1.106 ; 1.520)	
C_{max} (ng/mL)	11	3940	11	3460	1.138 (1.003 ; 1.291)	
Levodopa treatment difference (TRIGEL-Duodopa)						
Intra-individual fluctuation 0.5-14 h	11	0.823	11	0.749	0.074 (-0.088 ; 0.236)	
Intra-individual fluctuation 0.5-3h	11	0.649	11	0.688	-0.039 (-0.292 ; 0.214)	
Intra-individual fluctuation 3-14h	11	0.495	11	0.364	0.131 (0.052 ; 0.210)	
t_{max} (h)	11	14.2	11	10.9	3.342 (-0.499 ; 7.183)	
Carbidopa treatment ratio (TRIGEL/Duodopa)						
AUC_{0-14h}/dose (h*ng/mL/mg) [d]	11	22.1	11	18.8	1.178 (1.075 ; 1.291)	
AUC_{0-14h} (h*ng/mL)	11	4590	11	5110	0.898 (0.814 ; 0.989)	
AUC_{0-24h}/dose (h*ng/mL/mg) [d]	11	33.2	11	27.9	1.189 (1.100 ; 1.285)	
AUC_{0-24h} (h*ng/mL)	11	6880	11	7600	0.906 (0.830 ; 0.989)	
$AUC_{0.5-3h}$ (h*ng/mL)	11	717	11	825	0.869 (0.732 ; 1.033)	
AUC_{14-17h} (h*ng/mL)	11	1060	11	1200	0.877 (0.776 ; 0.991)	
AUC_{last}/dose (h*ng/mL/mg) [a,e]	11	28.1	11	24.0	1.169 (1.056 ; 1.295)	
AUC_{last} (h*ng/mL) [e]	11	5830	11	6540	0.891 (0.801 ; 0.991)	
CV 3-14 h (%)	11	10.3	11	12.5	0.824 (0.608 ; 1.115)	
C_{max} (ng/mL)	11	440	11	511	0.861 (0.766 ; 0.968)	
Carbidopa treatment difference (TRIGEL-Duodopa)						
Intra-individual fluctuation 0.5-14 h	11	0.708	11	0.740	-0.032 (-0.165 ; 0.101)	
Intra-individual fluctuation 0.5-3 h	11	0.523	11	0.534	-0.011 (-0.200 ; 0.178)	
Intra-individual fluctuation 3-14 h	11	0.405	11	0.440	-0.035 (-0.174 ; 0.103)	
t_{max} (h)	11	7.79	11	8.79	-1.004 (-4.585 ; 2.577)	
Entacapone [f]						
AUC_{0-14h}/dose (h*ng/mL/mg) [d]	6	5.73	N.A.	N.A.		
AUC_{0-14h} (h*ng/mL)	6	5290	N.A.	N.A.		
$AUC_{0.5-3h}$ (h*ng/mL)	6	1130	N.A.	N.A.		
AUC_{14-17h} (h*ng/mL)	6	602	N.A.	N.A.		
AUC_{last}/dose (h*ng/mL/mg) [d,e]	6	6.46	N.A.	N.A.		
AUC_{last} (h*ng/mL) [e]	6	5970	N.A.	N.A.		
CV 3-14 h (%)	6	18.8	N.A.	N.A.		
C_{max} (ng/mL) [g]	6	1580	N.A.	N.A.		
Intra-individual fluctuation 0.5-14 h	6	1.69	N.A.	N.A.		
Intra-individual fluctuation 0.5-3 h	6	1.22	N.A.	N.A.		
Intra-individual fluctuation 3-14 h	6	0.61	N.A.	N.A.		
t_{max} (h)	6	11.8	N.A.	N.A.		

[a] Results are presented as geometric least square mean (LSMean) values for AUCs, CV and C_{max} and arithmetic least square mean values for intra-individual fluctuations and t_{max}.
[b] Values are rounded to 3 significant figures.
[c] p-Value for test of treatment ratio (TRIGEL/Duodopa) for $AUC_{0-14h/dose}$ (h*ng/mL/mg) equal to 1.
[d] Administered doses of TRIGEL and Duodopa are presented in EOT Table 14.2.42 in CSR LSM-003 Module 5.3.3.2.1. The mean total dose of administered levodopa was 875 mg during TRIGEL and 1142 mg during Duodopa administration. The mean total dose of administered carbidopa was 219 mg during TRIGEL and 286 mg during Duodopa administration. The mean total dose of administered entacapone during TRIGEL administration was 875 mg.
[e] t_{last} are presented in EOT Table 14.2.9 (levodopa), EOT Table 14.2.21 (carbidopa) and EOT Table 14.2.40 (entacapone) in CSR LSM-003 Module 5.3.3.2.1.
[f] Results are presented as geometric least square mean values for AUCs, CV and C_{max} and arithmetic least square mean values for intra-individual fluctuations and t_{max}.
[g] Mean C_{max} for the entire time interval, the flush peak at 14 h is included.

Statistical analyses of 3-OMD PK parameters in study LSM-003

Parameter	TRIGEL		Duodopa		Treatment ratio/difference (95% CI)
	N	LSMean [a]	N	LSMean [a]	
Treatment ratio (TRIGEL/Duodopa)					
AUC $_{0\text{-}14h}$/dose (h*ng/mL/mg) [b]	11	155	11	131	1.181 (1.074 ; 1.299)
AUC $_{0\text{-}14h}$ (h*ng/mL)	11	129000	11	143000	0.900 (0.818 ; 0.991)
AUC $_{0.5\text{-}3h}$ (h*ng/mL)	11	27200	11	23600	1.150 (1.065 ; 1.242)
AUC $_{14\text{-}17h}$ (h*ng/mL)	6	21900	7	34800	0.631 (0.475 ; 0.836)
AUC $_{last}$/dose (h*ng/mL/mg) [b, c]	11	179	11	160	1.113 (0.988 ; 1.254)
AUC $_{last}$ (h*ng/mL) [c]	11	148000	11	175000	0.848 (0.750 ; 0.958)
CV 3-14 h (%)	11	10.5	11	7.44	1.405 (0.939 ; 2.103)
C_{max} (ng/mL)	11	11800	11	12600	0.938 (0.806 ; 1.091)
Treatment difference (TRIGEL-Duodopa)					
Intra-individual fluctuation 0.5-14 h	11	0.442	11	0.329	0.113 (-0.023 ; 0.249)
Intra-individual fluctuation 0.5-3 h	11	0.126	11	0.108	0.018 (-0.078 ; 0.114)
Intra-individual fluctuation 3-14 h	11	0.327	11	0.296	0.031 (-0.088 ; 0.149)
t_{max} (h)	11	0.479	11	13.4	-12.885 (-16.140 ; -9.630)

[a] Results are presented as geometric least square mean values for AUCs, CV and C_{max} and arithmetic least square mean values for intra-individual fluctuations and t_{max}. Values are rounded to 3 significant figures.
[b] Administered doses of levodopa during TRIGEL and Duodopa administration are presented in EOT Table 14.2.42 in CSR LSM-003, Module 5.3.3.2.1. The mean total doses of levodopa was 875 mg during TRIGEL and 1142 mg during Duodopa administration.
[c] t_{last} is presented in EOT Table 14.2.30 in CSR LSM-003, Module 5.3.3.2.1.

Source: EOT Table 14.2.32 in CSR LSM-003, Module 5.3.3.2.1

IV.3 Pharmacodynamics

Levodopa is a metabolic precursor of dopamine and mediates the anti-parkinsonian effect, whereas carbidopa and entacapone modify the peripheral metabolism of levodopa to increase and prolong brain exposure to levodopa and to diminish peripheral dopaminergic side effects. Overall, continuous delivery of LCIG provides lower variability in levodopa plasma concentrations compared to tablets. Several clinical studies have shown that LCIG therapy provides a decrease in both “off” time and dyskinesia in patients with advanced PD previously treated with oral formulations of levodopa.

IV.4 Clinical efficacy

The efficacy data is based on the results of the applicant-sponsored clinical pharmacokinetic LSM-003 study combined with literature data.

Study LSM-003
LSM-003 was not designed to compare the treatments with regard to clinical response as the patients were optimised with regard to dosing and clinical response on Duodopa, i.e. based on the patient’s pre-study optimised Duodopa dosing, but not on Lecigon.
The number of patients included in the study was very limited (n=11), and the observation period was short, 17 h, i.e. only one day. Therefore, the study lacks the statistical power to evaluate any change in clinical performance between Duodopa and Lecigon treatment. However, the Treatment Response Scale (TRS) (8) was used to assess the “on”/”off” effect with TRS ranging from -3 (severe “off”) to +3 (“on” with severe dyskinesia), where -1 to +1 is considered to be functional on-time.

Treatment Response Scale (TRS) data in study LSM-003

	Time period	LECIGON			Duodopa		
		"Off" [a] Mean % of time	**Functional "On" [b] Mean % of time**	**Dyskinesia [c] Mean % of time**	**"Off" [a] Mean % of time**	**Functional "On" [b] Mean % of time**	**Dyskinesia [c] Mean % of time**
All patients	0-3 h	28.8	68.1	3.1	8.6	89.8	1.6
	3-14 h	0.9	91.7	7.4	0.0	91.0	9.0
	14-17 h	3.5	90.8	5.8	0.0	88.0	12.0
Cohort 1 (morning dose of 80% of the corresponding Duodopa dose)	0-3 h	39.8	60.2	0.0	5.5	94.5	0.0
	3-14 h	0.1	99.9	0.0	0.0	100.0	0.0
	14-17 h	0.0	100.0	0.0	0.0	93.6	6.4
Cohort 2 (morning dose of 90% of the corresponding Duodopa dose)	0-3 h	19.6	74.7	5.7	11.3	85.9	2.9
	3-14 h	1.5	84.9	13.6	0.0	83.5	16.5
	14-17 h	6.4	83.1	10.6	0.0	83.3	16.7

[a] "Off": Troublesome OFF state, interferes with function and/or causes meaningful discomfort (score <-1).
[b] Functional "on": Near normal motor state, does not interfere with function or cause meaningful discomfort (-1≤score≤1).
[c] Dyskinesia: Troublesome dyskinesia, interferes with function and/or causes meaningful discomfort (score >1).
Calculation excludes all data after intake of night medication.

Efficacy Results in Studies Supportive of LCIG
Overall, continuous delivery of LCIG provides lower variability in levodopa plasma concentrations compared to sustained-release tablets. Several clinical studies have shown that LCIG therapy provides a decrease in both "off" time and dyskinesia.

Besides a large number of open-label studies, one randomised, controlled, double-blind, double-dummy study comparing LCIG with oral IR LC has been published by Olanov et al (2). This study demonstrated benefit with LCIG over oral IR LC. In this 12-week, randomised, double-blind, double-dummy clinical study comparing LCIG with oral IR LC, a statistically significant improvement in the LCIG group was observed for the Unified Parkinson's Disease Rating Scale (UPDRS) part II but not for the part III scores at 12 weeks. A reduction in "off"-time of 4.04 h was observed in the LCIG group (n=35) compared to a 2.14 h reduction in the oral IR LC group (n=31). Mean "on"-time without troublesome dyskinesia increased by 4.11 h in the LCIG group vs. 2.24 h in the oral IR LC group. These differences between the treatment groups in change from baseline to 12 weeks were statistically significantly in favour of LCIG. The decrease in "on"-time with troublesome dyskinesia was also in favour of LCIG but the difference between the treatment groups did not reach statistical significance. In the 52-week open-label extension of that study, during which all patients received LCIG, the authors conclude that improvements achieved during the first 12 weeks of treatment were sustained on long-term LCIG treatment (3).

The 54-week study published by Fernandez et al. (4) is the largest cohort to date of LCIG-treated patients. Continuous administration of LCIG led to a significant improvement in diary-assessed "off"-time of 4.4 h/day (65.6% increase), which was sustained throughout the 54-week trial. The reduction in "off"-time corresponded to a significant increase in "on"-time, without troublesome dyskinesia. Both the physician- and patient-perceived improvements were robust, with significant and enduring improvements in motor function as assessed by the UPDRS and Clinical global impression (CGI). Furthermore, total daily dosing, after initial titration/optimisation, was stable throughout the study, suggesting that patients did not develop tolerance to LCIG. Moreover, although adjunctive therapies were permitted after 28 days, there was low use of these therapies and 76.5% of patients remained on LCIG monotherapy.

The DuoCOMT was a study to investigate whether the levodopa dose could be reduced without worsening of motor fluctuations and levodopa concentration stability when oral COMT inhibitors (entacapone or tolcapone) are added to LCIG treatment. Patients were only studied a few days, and only 9 patients completed the study, making the clinical efficacy results, indicating that off"-time was not increased when decreasing the LCIG dose by 20%, difficult to draw any firm conclusion from.

In summary, the reduction in "off"-time in patients receiving LCIG in these studies was of a magnitude expected to be clinically meaningful to patients.

Efficacy Results in Studies Supportive of Oral LCE
In the 'SEESAW' study (5), the mean total daily levodopa dosage was approx. 100 mg or 12% lower in the LCE group than in the LC group (95% CI, 4-19%; p=0.003), with most of the decrease in dosage occurring during the first 4 weeks of entacapone treatment. The adjusted mean 3-OMD concentration was 57.8% lower in the LCE group than in the LC group (95% CI: 53.7-61.5; p<0.000l). The mean percent "on" time was significantly higher in the LCE group than in the LC group with an overall treatment effect of 5.0 percentage points (p=0.003) or approx. 1 h/day, and this effect was consistent across time (Weeks 8, 16, and 24). The effect of entacapone treatment was particularly prominent among patients who had a smaller percent "on" time (<55%) at baseline.
Entacapone had a beneficial effect on the total UPDRS score (p=0.05), reflected mainly in the motor (p=0.08) and ADL (p=0.06) subscales. The effect of entacapone on these scores tended to increase over time. At Week 24, the mean total UPDRS score had improved by 3.5 points in the LCE group compared to the LC group (p=0.018). There was no effect of entacapone treatment on the mental subscale score of the UPDRS. Entacapone increased mean asleep time by 15 min/day (p=0.05).
The beneficial effects of entacapone, as measured by percent "on"-time and UPDRS scores, were completely and rapidly lost on its withdrawal. In addition, 3-OMD values quickly returned to baseline levels in patients withdrawn from entacapone treatment.

Although it is difficult to perform a direct statistical comparison across published studies due to the large variation in follow-up periods (ranging from 1 day to several years) in the different studies, the published data (supportive studies and additional references) together with the results of the applicant-sponsored study LSM-003 support the proposed indication for Lecigon according to the applicant, i.e. treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyper-/dyskinesia when oral combinations of Parkinson medicinal products have not given satisfactory results.
The aim of the development of Lecigon was to improve the bioavailability of levodopa and thereby allow a dose reduction and potentially decrease the exposure to the metabolites and degradation products of levodopa-carbidopa.

Theoretical grounds for a decreased risk of polyneuropathy
The applicant has an additional discussion point of interest related to potential advantage of adding entacapone based on the conversion of levodopa into 3-OMD by COMT requires methyl groups supplied by S-adenosylmethionine, which is converted to S-adenosylhomocysteine and homocysteine. Homocysteine is re-methylated to methionine with folate as methyl group donor by methylenetetrahydrofolate reductase and vitamin B12. Doses of levodopa given in clinical practice increase the requirement of folate and vitamin B12 substantially. Since the supply of the methyl donors is limited, the potentially toxic homocysteine may increase and elevated plasma homocysteine is frequently reported in levodopa-treated patients. However, as the applicant also notes it is not clear whether homocysteine is a risk factor or a risk marker of pathology.

The applicant also discuss the relevance of catecholamine-O-methyl transferase (COMT) inhibition for decreased risk of neuropathy based on levodopa+carbidopa given in clinical practice increase the requirement of folate and vitamin B12 substantially, based on theoretical grounds as explained above. The applicant points out that during the past 10 years, attention has been drawn to an potential increased risk of neuropathy in patients with PD vs. healthy controls, especially in older age PD patients on long-term therapy with oral LC or patients with advanced PD treated with LCIG.

MPA agrees that there are theoretical grounds for a decreased risk of polyneuropathy by addition of entacapone to levodopa/carbidopa, and some clinical studies and observations that indicate such a positive effect, but a firm conclusion seems not possible based on the published data.

IV.5 Clinical safety

The safety data is based on the results of one applicant-sponsored clinical pharmacokinetic study LSM-003, combined with literature data on oral LCE, i.e. the same 3 substances as in Lecigon, and the intestinal gel with two of the substances (LC) in the same formulation. Lecigon is expected to have a similar safety profile as Duodopa combined with the safety profile for entacapone when used with oral LC.

In general, similar drug-related adverse events (AEs) occur when patients are treated with LC intestinal gel (LGIG) as when treated with oral LC formulations, but due to the route of administration, LCIG is also associated with complications related to the surgery or the device. Device- and procedure-related complications are the most frequently reported AEs including abdominal pain, excessive granulation tissue, complications of device insertion, incision site erythema, post procedural discharge, procedural pain, and procedural site reaction. Otherwise decreased weight, anxiety, depression, insomnia, dyskinesia, orthostatic hypotension, nausea, constipation, and fall are the most common drug-related AEs of LCIG.
The most common side-effects of entacapone are of dopaminergic character (dyskinesia, hallucinations), dependent of the concomitant use of levodopa. The second most common side-effects for entacapone are gastrointestinal symptoms (nausea, diarrhoea, vomiting) and harmless discoloration of the urine.

Study LSM-003
One clinical study (LSM-003) has been conducted with Lecigon. The primary objective of the study was to assess PK variables. The dose of levodopa was individualized and corresponded to 100% of the pre-study individually optimised dose. The Lecigon dose corresponded to 80% of the pre-study individually optimised dose of Duodopa. Safety assessments included AEs and incidents, physical examination, vital signs, electrocardiogram (ECG) and laboratory assessments. AEs were recorded during the short study period from initiation of infusion of the first study drug to the completion of the follow-up visit.

The 11 patients in the study received Lecigon and Duodopa on 2 consecutive days. A total of 16 AEs were reported in this study, whereof 10 AEs were reported by 6 patients (54.5%) on Lecigon and 6 AEs were reported by 2 patients (18.2%) on Duodopa. No serious or severe AEs were reported during the study and no AE led to study discontinuation or change in therapy.

Adverse events reported in study LSM-003 by system organ class and preferred term

System organ class Preferred term (PT)	LECIGON N=11		Duodopa N=11	
	No. of AEs	No. of patients (%)	No. of AEs	No. of patients (%)
Number of AEs	10	6 (54.5%)	6	2 (18.2%)
Gastrointestinal disorders				
Diarrhoea			1	1 (9.1%)
Nausea	1	1 (9.1%)	2	1 (9.1%)
General disorders and administration site conditions				
Injection site haematoma	3	1 (9.1%)	1	1 (9.1%)
Injury, poisoning and procedural complications				
Laceration	1	1 (9.1%)		
Nervous system disorders				
Dizziness	2	2 (18.2%)		
Headache	3	3 (27.3%)	1	1 (9.1%)
Skin and subcutaneous tissue disorders				
Cold sweat			1	1 (9.1%)

Unique adverse events assessed as at least possibly related to study drug, the pump or study procedure by system organ class and preferred term

System organ class	Preferred term (PT)	LECIGON (n=11) No. of unique AEs			Duodopa (n=11) No. of unique AEs		
		Study Drug	Study Pump	Study Procedure	Study Drug	Study Pump	Study Procedure
Gastrointestinal disorders	Diarrhoea				1 (9%)		1 (9%)
	Nausea	1 (9%)			1 (9%)		1 (9%)
General disorders and administration site conditions	Injection site haematoma			1 (9%)			1 (9%)
Nervous system disorders	Dizziness	1 (9%)					
	Headache	1 (9%)		3 (27%)			1 (9%)
Skin and subcutaneous tissue disorders	Cold sweat						1 (9%)
Unique AE = AE of a certain PT, counted only once within each patient and treatment arm.							

No statistical tests were performed for the safety variables. There were only minor changes in vital signs, ECG and physical examination during the study and no findings were assessed as clinically significant. The laboratory findings and AEs related to vital signs, physical findings and other observations related to Duodopa and entacapone are reflected in the proposed SmPC. No apparent differences in adverse events were observed between Duodopa and Lecigon groups. AEs assessed as related to Lecigon were headache, nausea and dizziness (one event each). No SAEs or severe AEs were reported during the study, no AEs led to study discontinuation or change in therapy, and no AEs were assessed to be related to the pump during Lecigon administration. Although the plasma concentrations of levodopa increased over time none of the patients reported hyperkinesia or other motor fluctuation during the study. However, due to the limited number of patients evaluated in this study, no safety conclusions can be based on these results.

The safety of Lecigon is expected to resemble Duodopa and the available levodopa / carbidopa / entacapone including products. The product information for Lecigon covers the safety profiles of products including LCIG and entacapone.

Studies providing safety data of LCE

The following 3 studies were the only identified studies which enrolled patients with advanced PD, and in which the active substances of any oral formulation in one study treatment arm were LCE (e.g. studies with unspecified DDCI instead of carbidopa did not qualify)

- The placebo-controlled, double-blind 'SEESAW' study (5) comparing oral LCE with oral LC.
- The randomised, prospective, open-label, parallel-group 'TC-INIT' study published by Brooks et al. (6) comparing a fixed oral combination of LCE (Stalevo) with oral IR LC plus adjunct entacapone.
- The randomised, double-blind, double-dummy, cross-over 'CLE with OLE' study, published by Stocchi et al. (7), comparing IR LC plus entacapone with extended-release (ER) LC.

No SAEs were reported in these studies. No pooled analyses have been performed. All AEs are reported in the publications by the Parkinson Study Group and Brooks et al.(6), while a cut-off limit of ≥2% was used for AEs in the publication by Stocchi et al. No tabulated data on laboratory values or vital signs are provided in these publications.

Studies providing safety data of LCIG

The presentation of safety data from the 3 studies providing safety data on LCIG is based on the safety data in the respective publication:

- The study published by Olanow et al. (2) was a 12-week study comparing LCIG with oral IR LC.
- The study published by Slevin et al. (3) was a long-term (52 weeks) open-label extension of the study by Olanow et al. (2), during which all patients received LCIG treatment
- The prospective, open-label, long-term (54 weeks) study published by Fernandez et al. (4) which is the largest (n=354) study with LCIG. Safety was the primary endpoint measured through AEs, device complications, and number of completers.

All AEs and SAEs are reported in the publications by Olanow et al.(2) and Slevin et al.(3), while a cut-off limit of ≥10% was used for AEs and of ≥1% for SAEs in the publication by Fernandez et al (4). No tabulated data on laboratory values or vital signs are provided in these publications.

Study Providing Safety Data on LCIG Plus Oral Entacapone

- In the DuoCOMT study all patients received their individually optimised doses of LCIG on Day 1 (baseline). Patients received oral entacapone (200 mg) or tolcapone (100 mg) on Days 2 and 3.

This study was not designed to evaluate safety of LCIG and no safety data were reported in the publication, however, the sponsor has received the collected AE data from the authors of the publication (Dag Nyholm; date of communication: 12–Nov-2015). No deaths or other serious adverse events (SAEs) occurred in this study. No laboratory values and no data on vital signs were provided.

Exposure

For Duodopa exposure data was provided in publications for up to 386 patients during 12 months mainly from open-label studies, while 103 patients were exposed to oral LCE and 102 patients were exposed to LC during 6 months in double-blind studies. No post-marketing data has been provided separately for the approved products. The mean daily dose of levodopa varied in these studies. The exposure in all studies is summarized in the table below.

Summary of exposure in supportive clinical studies:

Study	**LSM-003**		**DuoCOMT** [a] (1)		**Olanow 2014** (2)		**Slevin 2015** (3)	**Fernandez 2015** (4)	**SEESAW** (Parkinson Study Group 1997; 5)		**TC-INIT** (Brooks 2005; 6)		**CLE with OLE** (Stocchi 2014;7)	
Treatment	Lecigon	Duodopa	Duodopa + oral E	Duodopa	LCIG	Oral IR LC	LCIG	LCIG	LCE	LC	LCE	Oral IR LC + E	Oral IR LC + E	Oral ER LC
No. of exposed patients	11	11	10	11	37	34	62	354 (NJ) whereof 324 continued with PEG-J	103	102	83	94	88	110
Treatment duration	1 day	1 day	1 day	1 day	12 w	12 w	52 w	54 w	24 or 26 w	24 w	6 w	6 w	2 w	2 w
Mean (SD) daily levodopa dose (mg)	875.1 (253.1)	1142.2 (317.6)	1249	1760 (840) 1561 (590) when excluding a patient who only participated at the Duodopa BL recording	BL: 1005.4 (373.6) Increase from baseline: 91.7 (96.6)	BL: 1123.5 (477.9) Increase from baseline: 249.7 (94.9)	N.R. Patients recruited from both study arms in the study published by Olanow	BL: 1547.4 Last visit: 1572.4	BL: 791.0 (374.7) Last visit: approx. 100 mg (12%) lower than in the LC group.	BL: 752.1 (434.7)	BL: 493 (218)	BL: 472 (199)	652 (252)	1723 (713)
Mean (SD) daily entacapone dose (mg)	875.1 (253.1)	N.A.	400	N.A.	N.A.	N.A.	N.A.	N.A.	N.R.	N.A.	N.R.	N.R.	943 (174)	N.A.

[a] Treatment arm receiving Duodopa plus tolcapone not included in this table.
BL: Baseline; E: entacapone; NJ: nasojejunal administration; N.R.: Not reported; w: week.

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Adverse Events of LCIG (Duodopa)
Based on the Duodopa SmPC, the following PTs were reported by >10% of the patients in clinical studies (by SOC)

Drug-related AEs (to be differenced from device-related, regardless of causality assigned by the investigator):

- Metabolism and nutrition disorders: 'Weight decreased'
- Psychiatric disorders: 'Anxiety', 'Depression' and 'Insomnia'
- Nervous system disorders: 'Dyskinesia' and 'Parkinson's disease'
- Vascular disorders: 'Orthostatic hypotension'
- Gastro-intestinal disorders: 'Nausea' and 'Constipation'
- Injury, poisoning and procedural complications*:* 'Fall'

Device- and procedure-related AEs (regardless of causality assigned by the investigator)

- Infections and infestations: 'Postoperative wound infection'
- Gastro-intestinal disorders: 'Abdominal pain'
- Skin and subcutaneous tissue disorders: 'Excessive granulation tissue'
- General disorders and administration site conditions: 'Complications of device insertion'
- Injury, poisoning and procedural complications: 'Incision site erythema', 'Post procedural discharge', 'Procedural pain' and 'Procedural site reaction'.

A more detailed list of all AEs can be found in the Duodopa SmPC.

Adverse Event of Levodopa – Carbidopa - Entacapone (Stalevo)
Based on the SmPC for Stalevo, the following PTs (by SOC) were reported as very common (≥1/10) and more frequent with entacapone than with LC alone:
• Nervous system disorders: 'Dyskinesia'
• Gastrointestinal disorders: 'Diarrhoea' and 'Nausea'
• Musculoskeletal and connective tissue disorders: 'Muscle, musculoskeletal and connective tissue pain'
• Renal and urinary disorders: 'Chromaturia'
A more detailed list of all AEs can be found in the Stalevo SmPC.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan (version 1.0) , 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 Lecigon.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	□ Myocardial infarction and other ischaemic heart disease
Important potential risks	None
Missing information	□ Use in pregnancy and breast-feeding □ Clinical relevance of hydrazine content

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Myocardial infarction and other ischaemic heart disease	Proposed text in the SmPC: Section 4.3 "Contraindications, Section 4.4 "Special warnings and special precautions for use", 4.5 "Interaction with other medicinal products and other forms of interaction" and Section 4.8 "Undesirable effects" Prescription only medicine	Not applicable
Use in pregnancy and breast-feeding	Proposed text in the SmPC: Section 4.6 "Fertility, pregnancy and lactation" and Section 5.3 "Preclinical safety data" Prescription only medicine	Not applicable
Clinical relevance of hydrazine content	Proposed text in the SmPC: Section 4.4 "Special warnings and special precautions for use" and Section 5.3 "Preclinical safety data" Prescription only medicine	Not applicable

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly. The MPA considers the RMP acceptable.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Swedish.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Therapeutic Context
Disease or condition

The indication applied for by the Applicant is for “Behandling av Parkinsons sjukdom i komplikationsfas, med svårkontrollerade motoriska fluktuationer och hyperkinesi eller dyskinesi, när tillgängliga orala kombinationer av läkemedel mot Parkinsons sjukdom inte gett tillfredsställande resultat”.

The overall aim of continuous infusion of levodopa is to reduce severe motor fluctuations, which dramatically impair quality of life in PD patients on oral therapy. The background for this is that as the disease progresses the duration of benefit after a given dose of oral levodopa becomes progressively shorter and begins to mirror the t1/2 of levodopa. Patients begin to experience fluctuations in motor function alternating between “on” responses with a good anti-parkinsonian effect and “off” responses when levodopa does not adequately treat parkinsonian features. Patients can also experience involuntary movements or dyskinesia. These fluctuations in motor performance have been shown to a large extent correlate with the variation of levodopa plasma concentrations.

Available therapies and unmet medical need

Today, there are only three different treatments with continuous dopaminergic stimulation available for patients with advanced PD, who cannot be adequately treated with oral treatment at short intervals; Deep brain stimulation (DBS), s.c. apomorphine administration and levodopa-carbidopa intestinal gel (LCIG)(Duodopa). Complete amelioration of motor symptoms and dyskinesia is not obtained with any available treatment method in advanced PD and there are side effects, other disadvantages and contraindications to all three available treatments. Thus, there are still unmet medical needs in the treatment of patients with advanced PD.

Treatment with Lecigon is based on the same principle as Duodopa with a continuous duodenal/jejunal infusion of levodopa to obtain stable plasma concentrations of levodopa to reduce the motor fluctuations experienced with oral therapies. The main difference between Duodopa and Lecigon is that entacapone has been added with the hypothesis that this addition may improve the bioavailability of levodopa and thereby allow a dose reduction and potentially decrease the exposure to the metabolites and degradation products of levodopa-carbidopa.

Favourable effects

The Applicant has submitted literature data to support the beneficial effects of LCIG. Several clinical studies have shown that LCIG therapy provides a decrease in both “off” time and dyskinesia. Besides a large number of open-label studies, one randomised, controlled, double-blind, double dummy study comparing LCIG with oral IR LC has been published (2). This study demonstrated benefits with LCIG over oral IR LC. Literature data has also been submitted to support the benefits of oral triple combination of levodopa-carbidopa- entacapone compared to the combination levodopa-carbidopa. This treatment concept is well documented and combination products are approved in the EU.

The PK study performed by the Applicant has shown an increased bioavailability of levodopa when Lecigon is administered compared with Duodopa (AUC0 14h /dosage; 1, 38 [CI95 1,26-1,51]). This enables a reduction of the volume of Lecigon compared with that of Duodopa, making it possible to reduce the weight/size of the container. For patients not needing more than 940 mg levodopa per day one 50 mL Lecigon container would be enough for one days use, reducing the weight of the container by around 50% (approximately 50 g), compared with the Duodopa 100 mL cassette. The weight of the whole Lecig pump system with filled drug container (230g) is approximately 50% lower compared with the Duodopa pump (500g).The volume is also reduced by 50% (194cm3 versus 436 cm3). The estimated half-life of levodopa when administered as Lecigon is approximately 2 h. The half-life of levodopa is approximately 1.5 h when administered as Duodopa.

Uncertainties and limitations about favourable effects

No data has been submitted from clinical efficacy/safety studies to support the benefit of the triple combination of levodopa-carbidopa-entacapone administered as an intestinal gel. The benefits are only supported by the PK-study performed by the Applicant.

In the PK study, predicted levodopa plasma concentration time curve following Lecigon treatment is slightly different than the observed for Duodopa, where a gradual increase in the plasma concentration of levodopa during the day is expected following use of Lecigon. During the assessment rounds, the applicant presented an acceptable approach where the posology section in the SPC was revised to include further advice on how to individually adjust the pump to get the desired clinical response. This may in the individual patient possible be a more cumbersome titration compared to Duodopa. However, an adjustment of e.g. the flow rate during Lecigon treatment would not be very different from handling dose rate adjustment or bolus doses commonly applied during Duodopa treatment.

Cases of symptomatic polyneuropathy (PNP) have been reported in patients receiving Duodopa but also in patients with oral treatment. The polyneuropathy seems to be associated with high levodopa exposure and high age of the patients. Elevated levels of homocysteine have also been reported in those patients. The applicant argue that since conversion of levodopa to 3-OMD is a part of a cascade of events leading to vitamin B12, B 6 and/or folate deficiency and increased homocysteine, a reduction of the conversion of levodopa to 3-OMD caused by entacapone may reduce the risk of PNP. Accordingly, addition of entacapone to enteral levodopa/carbidopa could reduce the risk of PNP in patients with advanced PD treated with enteral levodopa/carbidopa.
Even though this hypothesis is interesting, it remains to be demonstrated in the clinical setting.

Treatment with Lecigon will reduce the hydrazine exposure compared with Duodopa. Although a reduction in the theory would be considered positive, the hydrazine levels are not below levels of concern, and the clinical benefit is of such a decreased exposure has not been demonstrated.

Unfavourable effects

Adding entacapone to Duodopa may result in an increased risk of adverse events and drug-drug interactions related to entacapone. An metaanalysis based on six studies (2.008 patients) indicated that those on levodopa/carbidopa/entacapone (LCE) had a higher risk of experiencing AEs compared to those on oral levodopa/dopa-decarboxylase inhibitors (levodopa/DDCI) (risk ratio 1.33; 95% CI: 1.05-1.70). There was no statistical significant difference in the risk of SAEs or discontinuation due to AEs (9), which is reassuring.

The most frequent adverse reactions reported for entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of treatment. Reduction of levodopa dosage decreases the severity and frequency of these reactions. The other major class of adverse reactions is gastrointestinal symptoms, including nausea, vomiting, abdominal pain, constipation and diarrhoea. Gastrointestinal symptoms are also commonly reported for levodopa/carbidopa. However there are some AE more frequent with use of entacapone than of levodopa /DDCI inhibitors (by frequency difference of at least 1% in the clinical data). Some of these AEs are muscle-, musculoskeletal and connective tissue pain, discolored urine (a harmless phenomenon), colitis, hepatic function test abnormal and hepatitis with mainly cholestatic features. The proposed SmPC of Lecigon complies with the SmPC of oral levodopa/carbidopa/entacapone which is agreed by the MPA.
Cardiac disorders are more common using entacapone than Duodopa, accordingly there is probably an increased risk using Lecigon compared with Duodopa. The incidence rates of myocardial infarction and other ischemic heart disease events (0,43% and 1,54% respectively) are derived from an analysis of 13 double- blind studies involving 2,082 patients with end-of-dose motor fluctuations receiving entacapone (see comments below under Uncertainties and limitations about unfavourable effects), (10).

The addition of entacapone to levodopa/carbidopa does not seem to add drug-drug interaction problems. However, due to entacapone´s affinity to cytochrome P450 2C9 in vitro there may be a potential to interfere with active substances whose metabolism is dependent on this isoenzyme such as S-warfarin. In an interaction study with healthy volunteers the INR values increased by 13%. A control of INR is recommended when entacapone is initiated for patients receiving warfarin. This is also reflected in the proposed SmPC for Lecigon,

Uncertainties and limitations about unfavourable effects

The main uncertainty is the limited safety data from clinical studies with the triple combination of levodopa/-carbidopa/-entacapone administered as an intestinal gel.

According to the last Entacapone PSUSA (Jan 2013 to Jan 2016) the outcome of one epidemiological study (COM998A2001) was that entacapone was not associated with an increased risk of myocardial infarction. The MAH shall reassess and conclude in a separate variation whether myocardial infarction should remain important potential- and identified risk for entacapone.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects
Continuous delivery of levodopa has been shown to be very effective in reducing the on/off phenomena in advanced Parkinson patients who are not well controlled with oral levodopa treatment. The aim of the development of Lecigon (levodopa-carbidopa-entacapone administered as an intestinal gel) was to improve the bioavailability of levodopa and thereby allow a dose reduction and potentially decrease the exposure to the metabolites and degradation products of levodopa-carbidopa.

The increased bioavailability of levodopa when Lecigon is administered compared with Duodopa makes it possible to reduce the weight and size of the device (container +pump) which is considered to be of substantial benefit for the patients. The wish of a smaller device is confirmed by an expert

committee and the president of the Swedish Parkinson´s Disease Association /Parkinsonförbunden, based on a question from the Applicant.

The addition of entacapone supports prolonged symptom control based on the longer half-life in situations when the continuous infusion needs to be interrupted. The prolonged time in "on-state" could help patients in many ADL situations, e.g. when dressing or undressing, when bathing or taking a shower. This should improve QoL and potentially also reduce the risks of e.g falls by reducing the risk of developing off symptoms before the pump is re-connected. Even though these benefits have not been confirmed in clinical efficacy trials, the well-known PK/PD profile of levodopa in the treatment of PD makes the benefits highly plausible.

The potential benefits of decreases of the exposure of metabolites and degradation products of levodopa-carbidopa have not been documented and remain hypothetical.

Medicinal products representing levodopa/carbidopa and entacapone, as well as combination of these substances, have been approved in the EU for many years. The cumulative exposure to Stalevo during the period from April 2003 through to September 2010 is estimated to be 1 137 509 patient years. Accordingly the safety profile may be considered as established, which is reassuring. The AE related to the triple combination administered as an intestinal gel is not expected to be substantially different compared with the approved oral formulation. The AEs related to the intra-duodenal/jejunal administration are also well known from Duodopa administration. Furthermore the individual tolerance to entacapone may be known, since use of an oral COMT inhibitor at introduction of Duodopa has been reported for 28% to 49% of patients (4, 11).

Balance of benefits and risks

Even though the benefits of adding entacapone to the well-known combination of levodopa-carbidopa in the context of administration as an intestinal gel are only supported by PK-data, these benefits (reduced weight and size of the device, extension of the time-interval for good motor performance during periods of pump disconnection) are expected to be of importance for patients in need of continuous levodopa treatment. The adverse events associated with the triple combination are well-known and are considered to be outweighed by the expected benefits.

Conclusion

Taken together, the MPA consider that Lecigon can be recommended for approval with the indication *"Behandling av Parkinsons sjukdom i komplikationsfas, med svårkontrollerade motoriska fluktuationer och hyperkinesi eller dyskinesi, när tillgängliga orala kombinationer av läkemedel mot Parkinsons sjukdom inte gett tillfredsställande resultat"*.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Lecigon, Intestinal gel, levodopa 20 mg/ml, carbidopa (monohydrate) 5 mg/ml, entacapone 20 mg/ml, was approved in the national procedure on 2018-10-04.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1986/01/MR	Initial Mutual Recognition Procedure	Yes	2019-09-24	Approval	N/A
SE/H/1986/01/E/01	Repeat-Use Procedure	No	2020-09-15	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)