19 September 2013
EMA/CHMP/707244/2013
Committee for Medicinal Products for Human Use (CHMP)

Levodopa Carbidopa Entacapone Sandoz

Levodopa Carbidopa Entacapone

Procedure No. EMEA/H/C/002785

Applicant: Orion Corporation

Assessment report for an initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification index
CEP	Certificate of suitability of European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
DDPS	Detailed Description of Pharmacovigilance System
DLP	Data Lock Point
EC	European Commission
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PL	Package Leaflet
RMP	Risk Management Plan
SPC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Orion Corporation submitted on 7 February 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levodopa/Carbidopa/Entacapone Sandoz, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2012.

The applicant applied for the following indication.

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

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from Orion Corporation allowing the cross reference to relevant quality, non-clinical and/or clinical data.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The cross-referred product Stalevo was given a Community Marketing Authorisation on 17 October 2008.

1.2. Manufacturers

Manufacturer responsible for batch release

Orion Corporation
Orionintie 1
Espoo
02200
Finland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola

Co-Rapporteur: Bruno Sepodes

CHMP Peer reviewer: N/A

PRAC Rapporteur: Kirsti Villikka

PRAC Co-Rapporteur: Maria Alexandra Pêgo

The EMA Product Team Leader: Pavel Balabanov

- The application was received by the EMA on 7 February 2013.
- The procedure started on 28 April 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 24 May 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 27 May 2013.
- The Joint Rapporteur/Co-Rapporteur Assessment Report was circulated to all CHMP members on 3 June 2013.
- The updated Joint Rapporteur/Co-Rapporteur Assessment Report was circulated to all CHMP members on 13 June 2013.
- During the CHMP meeting on 27 June 2013, the CHMP agreed on a List of Questions to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2013.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 August 2013.
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 5 September 2013.
- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Levodopa/Carbidopa/Entacapone Sandoz.

2. Scientific discussion

2.1. Introduction

This Marketing Authorisation Application concerns Levodopa/Carbidopa/Entacapone Sandoz for treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. It is a duplicate application to the marketing authorisation (MA) of Stalevo (MA no. EU/1/03/260/001-038).

The active substances are levodopa, carbidopa and entacapone (ATC code: N04BA03; Pharmacotherapeutic Group: Dopaminergic agents: Dopa and dopa derivatives).

The legal basis of this application was Article 10c of Directive 2001/83/ EC, Informed consent application, and accordingly a complete Module 1 is submitted. Letter of consent from the MAH of Stalevo was enclosed. The Applicant (Orion Corporation) is the marketing authorisation holder of the cross-referred medicinal product Stalevo. The Applicant had also obtained a MA for another duplicate of Stalevo, i.e. Levodopa/Carbidopa/Entacapone Orion.

The following information was updated compared to the approved information for the cross-referred medicinal product Stalevo:

- Stalevo does not have a Risk Management Plan (RMP) hence the RMP was presented in the current application.
- The Product Information of Levodopa/Carbidopa/Entacapone Sandoz is identical with the Product Information of Stalevo, except for the following: Annex III, Package leaflet: the local representatives.

2.2. Quality aspects

Since this application is an informed consent of the Stalevo application, the quality data in support of the Levodopa/Carbidopa/Entacapone Sandoz are identical to the up-to-date quality data of the Stalevo dossier, which have been assessed and approved, including all post-marketing procedures.

2.3. Non-clinical aspects

This application was an informed consent application and no new non-clinical data was submitted. Therefore, the non-clinical data for Levodopa/Carbidopa/Entacapone Sandoz refers to and are identical to the up-to-date non-clinical data of the Stalevo dossier.

2.4. Environmental risk assessment

Since this application is an informed consent application , the medicinal product subject to this application is intended to be administered at comparable dose levels and for indications that were already approved in the Union for Stalevo. Based on the assumption that the levodopa/carbidopa/entacapone film-coated tablet was intended to substitute for identical products on the market, the approval of the product should not result in an increase of the total quantity of the active ingredients released into the environment. Therefore, it should not result in an increase of risk to the environment during storage, distribution, use and disposal. Reference is therefore made to the

Environmental risk assessment of the marketing authorisation application of the original medicinal product Stalevo (MA no. EU/1/03/260/001-038).

In order to enhance the protection of the environment, a general statement for the appropriate disposal of the unused medicinal product was included to the PL:

"*Medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.*"

2.5. Clinical aspects

This application is an informed consent application and no additional clinical studies have been provided. Therefore, the clinical data for Levodopa/Carbidopa/Entacapone Sandoz refers to and are identical to the up-to-date clinical data of the Stalevo dossier. For Clinical Overviews and Clinical Summaries please refer to Stalevo assessment reports EMEA/H/C/000511.

2.5.1. Pharmacokinetics

Levodopa. Absorption of levodopa is relatively poor (15–33 %) and food may delay or reduce absorption of levodopa. Half-life of levodopa is about 0.6–1.3 hours. No accumulation of levodopa is expected in repeated administration. Levodopa is extensively metabolised by dopadecarboxylase and by catechol-O-methyltransferease.

Carbidopa. Absorption of carbidopa is somewhat slower than levodopa Tmax being about 1 hour. Bioavailability of carbidopa is about 40–70 %. There are two main metabolites for carbidopa and approximately 30 % of carbidopa dose are excreted unchanged in urine.

Entacapone. Entacapone is absorbed rapidly and peak concentrations are achieved about one hour after dosing. Pharmacokinetics is linear and peak concentrations increase proportionally with the dose. Elimination half-life of entacapone is short (ß-phase about 0.5 h and γ-phase 2.4 h). The first-pass metabolism of entacapone is extensive and bioavailability is only about 35 %. Large inter- and individual variability is seen in the peak concentrations of entacapone but there seems to be no accumulation of entacapone during repeated administration. Food does not affect absorption of entacapone.

Entacapone is distributed largely and the volume of distribution is about 180 l. The total plasma clearance is about 800 ml/min. Entacapone is largely bound to plasma proteins, mainly to albumin.

Entacapone is almost completely metabolised prior to excretion and only about 0.2% of the dose is found unchanged in urine. The main metabolic pathways are glucuronidation of entacapone and a small amount of entacapone, the (E)-isomer, is converted to its (Z)-isomer. The active metabolite of entacapone, the (Z)-isomer, accounts for about 5% of the total amount in plasma. About 10% of entacapone dose is excreted in urine and the rest is eliminated via faeces by biliary excretion.

2.6. Pharmacovigilance system

The summary of pharmacovigilance system was provided in module 1.8.1. of the dossier including information required according to Article 8(3)(ia) of Directive 2001/83/EC i.e. contact details of the Qualified Person for Pharmacovigilance) and the location of the Pharmacovigilance System Master File (with the QP). Documentation also contained a statement signed by the MAH and the QPPV to the

effect that the MAH had the necessary means to fulfil the tasks and responsibilities listed in the Title IX of the Directive 2001/83/EC.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1, the PRAC considers by consensus that the risk management system for levodopa, carbidopa and entacapone (Levodopa/Carbidopa/ Entacapone Sandoz) for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment could be acceptable provided an updated risk management plan and satisfactory responses to the List of Questions provided below are submitted.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Rhabdomyolysis, NMS, Liver and biliary system disorders and liver laboratory abnormalities
Important potential risks	Severe skin and severe allergic reactions, Myocardial infarction and other ischaemic heart disease, Prostate cancer, Medication residue
Missing information	Pregnancy

The PRAC considered that the summary of safety concern should be updated to reflect the list of recommended changes listed at the end of this section.

- **Pharmacovigilance plans**

Table 2.2: Ongoing and planned studies in the PhV development plan

Activity/Study title (type of activity, study title category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Epidemiological study: The risk of developing prostate cancer (PCA) in entacapone and levodopa/DDCI users compared to levodopa/DDCI users without entacapone (noninterventional, 3)	To compare the PCA incidence rates between patients on levodopa/DDCI with entacapone +/- dopamine agonists (DA) and/or monoamine oxidase B (MAOB) inhibitors and patients on levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitors	Prostate cancer	Proposed protocol submitted to FDA	Under discussion
Epidemiological study: The risk of incident myocardial infarction in addon entacapone to levodopa/DDCI users compared to other add-on Parkinson's disease therapy users without entacapone (noninterventional, 3)	To estimate the incidence rate of myocardial infarction in subjects with add-on entacapone and to compare it with that of nonusers of entacapone	Myocardial infarction	Proposed protocol submitted to FDA	Under discussion

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan was sufficient to identify and characterise the risks of the product, but the recommendations given below were to be considered.

The PRAC also considered that routine PhV was sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Rhabdomyolysis	**1. (Proposed) text in SmPC** • *Section 4.3 Contraindications:* A previous history of neuroleptic malignant syndrome (NMS) and/ or nontraumatic rhabdomyolysis are mentioned as contraindications • *Section 4.4 Special warnings and precautions for use:* Warning and information about risk of rhabdomyolysis and neuroleptic malignant syndrome is given. • *Section 4.8 Undesirable effects:* Rhabdomyolysis and neuroleptic malignant syndrome are mentioned as adverse reactions. **2. Other routine risk minimisation measures** • Close monitoring through routine pharmacovigilance **3. Prescription only medicine**	None proposed.
Important identified risk: Neuroleptic malignant syndrome (NMS)	• *Section 4.3 Contraindications:* A previous history of neuroleptic malignant syndrome (NMS) and/ or nontraumatic rhabdomyolysis are mentioned as contraindications • *Section 4.4 Special warnings and precautions for use:* Warning and information about risk of rhabdomyolysis and neuroleptic malignant syndrome is given. • *Section 4.8 Undesirable effects:* Rhabdomyolysis and neuroleptic malignant syndrome are mentioned as adverse reactions. **2. Other routine risk minimisation measures** • Close monitoring through routine pharmacovigilance **3. Prescription only medicine**	None proposed.
Important identified risk: Liver and biliary system disorders and liver laboratory abnormalities	**1. (Proposed) text in SmPC** • *Section 4.2 Posology and method of administration / hepatic impairment:* Warning about the use in patients with mild to moderate hepatic impairment is given. Dose reduction may be needed.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• *Section 4.3 Contraindications:* Severe hepatic impairment is mentioned as a contraindication • *Section 4.4 Special warnings and precautions for use:* Periodic evaluation of hepatic, function is recommended during extended therapy with Levodopa/Carbidopa/Entacapone Sandoz and in patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time. • *Section 4.8 Undesirable effects:* Hepatic function tests abnormal and Hepatitis with mainly cholestatic features are mentioned as adverse reactions. • *Section 5.2 Pharmacokinetic properties / Characteristics in patients /hepatic impairment:* Summary of entacapone pharmacokinetics in hepatic impairment is given. **2. Other risk minimisation measures** • Close monitoring through routine pharmacovigilance **3. Prescription only medicine**	
Important potential risk: Severe skin and severe allergic reactions	**1. (Proposed) text in SmPC** • *Section 4.3 Contraindications:* Hypersensitivity to the active substances or to any of the excipients is mentioned as a contraindication. • *Section 4.8 Undesirable effects:* Rash, angioedema and urticaria are mentioned as adverse reactions. **2. Other risk minimisation measures** • Close monitoring through routine pharmacovigilance **3. Prescription only medicine**	None proposed.
Important potential risk: Myocardial infarction and other ischaemic heart disease	**1. (Proposed) text in SmPC** • *Section 4.4 Special warnings and precautions for use:* Warnings about administrations in patients with ischemic heart disease or history of myocardial infarction are given. Recommendation of periodic evaluation of cardiovascular function in extended therapy is	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	stated. • *Section 4.8 Undesirable effect:* Ischaemic heart disease events other than myocardial infarction (e.g. angina pectoris), irregular heart rhythm and myocardial infarction are presented as adverse effects. **2. Other risk minimisation measures** • Close monitoring through routine pharmacovigilance **3. Prescription only medicine**	
Important potential risk: Prostate cancer	**1. (Proposed) text in SmPC** • None proposed **2. Other risk minimisation measures** Close monitoring through routine pharmacovigilance	None proposed.
Important potential risk: Medication residue	**1. (Proposed) text in SmPC** • None proposed **2. Other risk minimisation measures** Close monitoring through routine pharmacovigilance	None proposed.
missing information: Pregnancy	**1. (Proposed) text in SmPC** • *Section 4.6 Fertility, pregnancy and lactation:* It is stated that there are no adequate data of the use during pregnancy. **2. Other risk minimisation measures** • Close monitoring through routine pharmacovigilance **3. Prescription only medicine**	None proposed.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures were sufficient to minimise the risks of the product in the proposed indication, but the recommendations given below were to be considered.

In addition, the PRAC made several comments and requested that an update of the Risk management Plan is to be submitted to take the following minor points into consideration:

1. The Applicant should revise the RMP module SVII "Important identified and potential risks" and RMP module SVIII "Summary of the safety concerns" to better reflect the known safety profile of the product and the sections 4.4. and 4.8. of the SmPC, and consider any risk that could have an impact on the risk-benefit balance of the product or have implications for public health as important.

The Applicant should provide detailed risk data, e.g. frequency, public health impact, impact on the individual patient, risk factors, preventability, potential mechanism, evidence source and strength of the evidence, and provide a justification for the classification as an important identified vs. potential risk.

In addition to the safety concerns already listed in the summary of safety concerns, the Applicant should consider, but not necessarily be limited, to the following additional important identified risk:

- Depression with suicidal tendencies
- Impulse control disorders
- Thrombocytopenia
- Gastrointestinal haemorrhage
- Colitis
- Orthostatic hypotension

Furthermore, the risk of myocardial infarction and other ischaemic heart disease that is currently reported as a potential risk should be described as an important identified risk.

Since seven strengths of the product will become available, medication error should be included as a potential risk. On the other hand, medication residue should not be considered as an important risk and should be removed from the RMP.

2. The Applicant should revise the RMP Part III "Pharmacovigilance Plan" to reflect the changes requested and made to the RMP modules SVII "Important identified and potential risks" and SVIII "Summary of safety concerns".

3. The Applicant should revise the RMP Part V "Risk minimisation measures" to reflect the changes requested and made to the RMP modules SVII "Important identified and potential risks" and SVIII "Summary of the safety concerns".

4. The Applicant should revise the Summary of the RMP to reflect the changes requested and made to the RMP.

5. Since the epidemiological studies on prostate cancer and myocardial infarction are included in the EU-RMP, the study protocols should also be included in Annex 6 of the RMP."

The Applicant responded to the request and provided an updated RMP.

In the updated RMP, version 1.1, the Applicant had listed the following safety concerns:

Table 4: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Rhabdomyolysis, NMS, Liver and biliary system disorders and liver laboratory abnormalities, Impulse control disorders, Depression with suicidal tendencies, Gastrointestinal haemorrhage, Colitis, Thrombocytopenia, Orthostatic hypotension, and Myocardial infarction and other ischaemic heart disease
Important potential risks	Severe skin and severe allergic reactions, Prostate cancer, Medication Error
Important missing information	Pregnancy

The RMP Part III "Pharmacovigilance Plan", the RMP Part V "Risk minimisation measures" and the Summary of the RMP were adequately updated according to the changes made to the safety concerns.

It was requested that the Applicant add to the Part V and Part VI of the RMP for thrombocytopenia the following text in the SmPC that is presented as a routine risk minimization measure for liver and biliary system disorders and liver laboratory abnormalities, and myocardial infarction and other ischemic heart disease, and also applies for thrombocytopenia:

"Section 4.4 Special warnings and precautions for use: Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Levodopa/Carbidopa/ Entacapone Sandoz."

According to the GVP Module V - Risk management systems, a summary of the RMP should be made publically available and should be written for the lay reader to fulfill the principles of transparency in the legislation. Therefore, the Applicant was required to provide explanations for the abbreviations and terms used in the Summary of the RMP that are not commonly known, such as DDCI (dopa decarboxylase inhibitor).

The above mentioned changes could be regarded as minor stylistic changes and did not require further assessment.

The CHMP endorsed this advice without changes.

2.8. User consultation

The applicant enclosed the user testing report performed for the combined PL of Stalevo 50/12.5/200 mg, 100/25/200 mg and 150/37.5/200 film-coated tablets. The PL version tested was the PL submitted in connection with Stalevo renewal application (EMEA/H/C/511/R/040). The conducted readability testing was considered acceptable in CHMP opinion (EMEA/498045/2008) on 25 September 2008.

The proposed PL of the duplicate was identical with Stalevo PL. The applicant considered that no separate user testing for the duplicate PL was necessary, and this was endorsed by the CHMP.

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The marking was considered adequate.

3. Benefit-Risk Balance

3.1. Final overall conclusion and risk benefit assessment

Since this application for Levodopa/Carbidopa/Entacapone Sandoz was submitted in accordance with Article 10c of Directive 2001/83/EC, as amended (Informed Consent Application). the CHMP had previously reviewed data on quality, safety and efficacy in the context of Stalevo application. Furthermore, the Applicant provided adequate responses to the CHMP and PRAC questions related to the environmental risk assessment and to the risk management plan. Therefore the CHMP considered that the benefit-risk balance of Levodopa/Carbidopa/Entacapone Sandoz was favourable and recommended the granting of the marketing authorisation for the following indication:

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

4. Recommendations

Conditions and requirements of the Marketing Authorisation

Medicinal product subject to medical prescription.

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web portal.

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- 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.