

Public Assessment Report

Scientific discussion

Levodopa/Carbidopa/Entacapone Sigillata (levodopa/carbidopa/entacapone)

SE/H/1391/01-07/DC

**This module reflects the scientific discussion for the approval of
Levodopa/Carbidopa/Entacapone Sigillata. The procedure was finalised at 2014-08-06.
For information on changes after this date please refer to the module 'Update'.**

I. INTRODUCTION

The application for Levodopa/Carbidopa/Entacapone Sigillata, 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200 mg, 175/43.75/200 mg, 200/50/200 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Sigillata Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and concerned member states (CMS) BE, ES, FR, LU, PT and SK.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Stalevo, 50 mg/12.5 mg/200 mg, film-coated tablets, authorised via the centralised procedure in 2003, with Orion Corporation, Finland, as marketing authorisation holder.

The reference product used in the bioequivalence study is Stalevo, 50 mg/12.5 mg/200 mg, film-coated tablets, with member state of source Iceland and Stalevo, 200 mg/50 mg/200mg, film-coated tablets, member state of source Germany, both with Orion Corporation, Finland as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Levodopa/Carbidopa/Entacapone Sigillata, is presented in the form of film coated tablets containing fixed combinations of the three substances levodopa, carbidopa and entacapone in seven strengths, 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200 mg, 175/43.75/200 mg and 200/50/200 mg. The excipients are ethanol 96%, croscarmellose sodium, hydroxypropylcellulose, trehalose dihydrate, cellulose, sodium sulfate, anhydrous, cellulose, microcrystalline and magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, macrogol, lecithin (soya) iron oxide red and iron oxide yellow. The tablets are packed in HDPE containers sealed with an aluminium foil and closed with a PP lid.

II.2 Drug Substance

Levodopa, carbidopa and entacapone have a monograph in the Ph Eur. Levodopa is a white or almost white crystalline powder, slightly soluble in water, carbidopa is white or yellowish white powder, slightly soluble in water and entacapone is greenish or yellow powder, practically insoluble in water. The structures of levodopa, carbidopa and entacapone have been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Levodopa/Carbidopa/Entacapone Sigillata, film coated tablets are formulated using excipients described in the current Ph Eur, except for the colouring agents iron oxide red and iron oxide yellow which are controlled according to acceptable NF monograph. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone. When given separately without the two other active substances, the bioavailability for levodopa is 15-33%, for carbidopa 40-70% and for entacapone 35% after a 200 mg oral dose. Following an oral dose of Stalevo maximal plasma concentrations of levodopa, carbidopa and entacapone occur at approximately 1.5 hours, 3 hours and 1 hour respectively. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa. Food does not significantly affect the absorption of entacapone. There are no restrictions with respect to food in the SmPC of the originator. The terminal half-life is 0.6-1.3 hours for levodopa, 2-3 hours for carbidopa and 0.4-0.7 hours for entacapone, each given separately.

Bioequivalence of the applied product was evaluated in two pivotal single-dose, two-way crossover partial replicated studies under fasting conditions:

Study 2218/10 with the 50 mg/12.5 mg/200 mg strength

Study 2219/10 with the 200 mg/50 mg/200 mg strength

In addition, two pilot studies were performed in order to decide what test formulation to proceed with.

Study 2218/10 was conducted in 84 healthy volunteers, comparing

Levodopa/Carbidopa/Entacapone, 50 mg/12.5 mg/200 mg, film-coated tablets, manufactured by FHI Zdravlje, Serbia with Stalevo, 50 mg/12.5 mg/200 mg, film-coated tablets, by Orion corporation, Finland, from the Icelandic market. The study was conducted at Lotus Labs Pvt. Ltd., Bangalore, India between 16th and 30th April 2011. Blood samples were collected pre-dose and up to 16 hours post-dose. The study design is considered acceptable. Plasma concentrations of levodopa, carbidopa and entacapone were determined with adequately validated LC/MS/MS methods. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for levodopa, carbidopa and entacapone.

Study 2219/10 was conducted in 84 healthy volunteers, comparing Levodopa/carbidopa/entacapone, 200 mg/50 mg/200 mg, film-coated tablets, manufactured by FHI Zdravlje, Serbia with Stalevo, 200 mg/50 mg/200 mg, film-coated tablets, by Orion Corporation, Finland from the German market. The study was conducted at Lotus Labs Pvt. Ltd., Bangalore, India between 22nd June and 4th 2011. Blood samples were collected pre-dose and up to 16 hours post-dose. The study design is considered acceptable. Plasma concentrations of levodopa, carbidopa and entacapone were determined with adequately validated LC/MS/MS methods. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for levodopa and carbidopa. For entacapone, the 90% confidence interval for the ratio of the test and reference products for AUC_{0-t} fell within the conventional acceptance range of 80.00-125.00%. However, for C_{max} the confidence interval was just outside the conventional acceptance range (90% CI: 79.37-103.59). The intra-individual variability of C_{max} for the reference product in this partial replicated study was 37.20, which allows a widening of the acceptance range for C_{max} to 76.06-131.47%. The widening of the acceptance range for entacapone C_{max} has been sufficiently justified.

Thus, bioequivalence has been demonstrated for the 50 mg/12.5 mg/200 mg strength and for the 200 mg/50 mg/200 mg strength.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 English.

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.

The results of the conducted bioequivalence studies can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Levodopa/Carbidopa/Entacapone Sigillata, 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200mg, 100 mg/25 mg/200mg, 125 mg/31.25 mg/200mg, 150 mg/37.5 mg/200mg, 175 mg/43.75 mg/200 mg, 200 mg/50 mg/200mg, film-coated tablets, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Levodopa/Carbidopa/Entacapone Sigillata, 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200mg, 100 mg/25 mg/200mg, 125 mg/31.25 mg/200mg, 150 mg/37.5 mg/200mg, 175 mg/43.75 mg/200 mg, 200 mg/50 mg/200mg, film-coated tablets, was successfully finalised on 2014-08-06.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)