LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Carbidopa/Levodopa Fair-Med
(carbidopa, levodopa)

SE/H/1413/01-04/DC

This module reflects the scientific discussion for the approval of Carbidopa/Levodopa Fair-Med. The procedure was finalised on 2016-01-21. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Carbidopa/Levodopa Fair-Med, 12,5 mg/50 mg, 10 mg/100 mg, 25 mg/ 100 mg, 25 mg/250 mg, tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Fair-Med Healthcare GmBH applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, DE, DK, FI, IE, MT, NL, NO, PT and UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Sinemet, 10 mg/100 mg, tablets, authorised in UK since 1973, with Merck Sharp & Dohme Limited as marketing authorisation holder.
The reference products used in the bioequivalence studies are Sinemet, 25 mg/250 mg, tablets and Sinemet Plus 25 mg/100 mg, tablets from UK with Merck Sharp & Dohme Limited as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

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 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

To support the application, the applicant has submitted two bioequivalence studies under fasting conditions, described below.

Pharmacokinetic study on the 25mg/250mg strength (Study 061-13)

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 54 healthy male volunteers, comparing Carbidopa/Levodopa, 25mg/250mg, tablet with Sinemet, 25mg/250mg, tablet under fasting conditions. The study was conducted at AXIS Clinicals Limited in India between 19/02/13 and 28/02/13. Blood samples were collected pre-dose and up to 16 hours post-dose. The study design is considered acceptable. Plasma concentrations of carbidopa and levodopa were determined with a LC/MS/MS method. 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 both Carbidopa and Levodopa.

Pharmacokinetic study on the 25mg/100mg strength (Study 670-13)

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 50 healthy male volunteers, comparing Carbidopa/Levodopa, 25mg/100mg, tablet with Sinemet Plus, 25mg/100mg, tablet under fasting conditions. The study was conducted at AXIS Clinicals Limited between 09/01/14 and 19/01/14. Blood samples were collected pre-dose and up to 16 hours post-dose. The study design is considered acceptable. Plasma concentrations of Carbidopa and Levodopa were determined with an LC/MS/MS method. 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 both Carbidopa and Levodopa.

The 10mg/100mg strength is to be waived based on the bioequivalence study performed on the 25mg/250mg tablet and the strength 12.5mg/50mg is to be waived based on the bioequivalence study performed on the 25mg/100mg tablet. In the EPAR for Stalevo it is stated that in the presence of carbidopa, levodopa follows linear pharmacokinetic. In a between- study-comparison of the two bioequivalence studies submitted by the applicant, the data follow a dose-proportional relationship in AUC following a 100mg and 250mg dose of levodopa. Thus, the data all together do not point out that there should be a less than proportional increase in AUC with increasing dose of levodopa, which would be the only case where a study with the lower strengths in each strength pair would be necessary. Thus, the biowaiver for the two lower strengths, 10mg/100mg and 12.5mg/50mg, can be accepted.

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.

IV.3 Risk Management Plan

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

MAA has submitted an updated RMP according to RMS comments.

Safety concerns:

Important identified risks	Dyskinesias Psychosis associated events Impulsive control disorders Orthostatic hypotension Sudden onset of sleep Neuroleptic malignant syndrome
Important potential risks	Malignant melanoma
Missing information	None

Routine pharmacovigilance is proposed and regarded as sufficient.
No addidional pharmacovigilance activities are proposed which is endorsed.

The RMP is considered approvable.

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 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Carbidopa/Levodopa Fair-Med, 12,5 mg/50 mg, 10 mg/100 mg, 25 mg/ 100 mg, 25 mg/250 mg, tablets, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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

The Mutual recognition/Decentralised procedure for Carbidopa/Levodopa Fair-Med, 12,5 mg/50 mg, 10 mg/100 mg, 25 mg/ 100 mg, 25 mg/250 mg, tablets, was positively finalised on 2016-01-21.

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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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se