LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tremopen
(carbidopa monohydrate, levodopa)

SE/H/1970/01-04/DC

This module reflects the scientific discussion for the approval of Tremopen. The procedure was finalised on 2021-11-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Tremopen, 12,5 mg/50 mg, 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg, Tablet.

The active substances are levodopa and carbidopa monohydrate. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Tremopen, 12.5 mg/50 mg, 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Fairmed Healthcare GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE, EE, ES, FI, IT, LT, LV, NL and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Sinemet, 12.5 mg/50 mg, tablet, authorised in UK since 1988, with Merck Sharp & Dohme Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Sinemet 25 mg/250 mg, tablet and Sinemet 25 mg/100 mg, tablet, from UK with Merck Sharp & Dohme Limited as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in some CMS.

- AT, DE, ES: Sinemet 12,5 mg/50 mg, tablet, authorised in SE since 1988
- AT, DE, ES, FI: Sinemet 10 mg/100 mg, tablet, authorised in SE between 1975 and 2013
- LV, PL: Sinemet, 25 mg/100 mg, tablet, authorised in SE since 1988
- LV, PL: Sinemet 25 mg/250 mg, tablet, authorised in SE between 1975 and 2013

Merck Sharp & Dohme BV is marketing authorisation holder for all four.
The justification to use this product is based on RMS's own files.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of carbidopa and levodopa are well known. As carbidopa and levodopa are widely used, well-known active substances, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Tremopen is intended for generic substitution, this will not lead to an increased exposure to the environment. Although the reference product Sinemet is not approved in all CMS, other carbidopa/levodopa products are approved, and a potential additional increased exposure to the environment from approval of Tremopen is considered insignificant. Therefore, an environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Tremopen from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Carbidopa/Levodopa with the reference product Sinemet.

Pharmacokinetic properties of the active substance
Absorption: Levodopa is rapidly and completely absorbed, but undergoes extensive first pass metabolism. The bioavailability of levodopa is approximately 30% without co-administration of carbidopa. Maximal plasma concentrations of levodopa occur approximately 45 minutes after dose administration.

Four degradation pathways are known where decarboxylation of levodopa to dopamine is the most important. Carbidopa inhibits the peripheral decarboxylation of levodopa, whereby plasma and urinary concentrations of dopamine is reduced. The plasma concentration of levodopa is then increased 4-5 times.

Elimination: The terminal half-life is approximately 1 hour for levodopa and 2-3 hours for carbidopa. The half-life of levodopa is not appreciably affected by co-administration of carbidopa.

There are no restrictions with respect to food in the SmPC of the originator Sinemet.

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, 25 mg/250 mg, tablet with Sinemet, 25 mg/250 mg, 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, 25 mg/100 mg, tablet with Sinemet Plus, 25 mg/100 mg, 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.

Discussion and overall conclusion
The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

The 10 mg/100mg strength is to be waived based on the bioequivalence study performed on the 25 mg/250 mg tablet and the strength 12.5 mg/50 mg is to be waived based on the bioequivalence study performed on the 25 mg/100 mg 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 100 mg and 250 mg 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, 10 mg/100 mg and 12.5 mg/50 mg, can be accepted from a pharmacokinetic perspective.

Based on the submitted bioequivalence studies, Tremopen is considered bioequivalent with Sinemet.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted an updated 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 Tremopen.

In line with the updated GVP module V rev 2, the RMP should focus on the important identified risks that are likely to have an impact on the risk-benefit balance of the product, which would usually warrant further evaluation as part of the pharmacovigilance plan and risk minimisation activities, e.g., product information advising on specific clinical actions to be taken to minimise the risk or additional risk minimisation activities. The SmPC for the product already contains the common warnings for Anti-Parkison drugs, dopaminergic agents, and additional monitoring and/or risk minimisation activities are not warranted.

Table SVIII.1: Summary of safety concerns

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

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

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

Summary of the RMP
The submitted updated **Risk Management Plan, version 03 signed 21st September 2021** is updated in line with the product Carbidopa/Levodopa Fair-med and **is considered acceptable**.

An updated RMP should be submitted:
- At the request of the RMS;
- 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 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 quality of the generic product, Tremopen is found adequate. There are no objections to approval of Tremopen, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

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

Post approval commitments

Commitment for CMS PL:
The applicant commits to provide valid QP declarations based on valid audit reports as soon as the audit of the manufacturer has been conducted.

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

N/A

VII. APPROVAL

The decentralised procedure for Tremopen, 12,5 mg/50 mg, 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg, tablet was positively finalised on 2021-11-11.

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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

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

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