LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Levodopa/Benserazide Owlpharma
(levodopa, benserazide hydrochloride)

SE/H/2111/01/DC

This module reflects the scientific discussion for the approval of Levodopa/Benserazide Owlpharma. The procedure was finalised on 2021-10-06. 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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Levodopa/Benserazide Owlpharma, 100 mg/25 mg, Tablet.

The active substances are levodopa and benserazide hydrochloride. 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 Levodopa/Benserazide Owlpharma, 100 mg/25 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Owlpharma - Consulting, Lda., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FI as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Madopark, 100 mg/25 mg, tablet authorised in Sweden since 1988, with Roche AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Madopar, 250 mg (200 mg/50 mg), tablet from Germany with Roche as marketing authorisation holder.

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 levodopa and benserazide are well known. As levodopa and benserazide are widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Levodopa/Benserazide Owlpharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Levodopa/Benserazide Owlpharma from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Levodopa/Benserazide with the reference product Madopar.

Pharmacokinetic properties of the active substance
Benserazide
Absorption: About 70 % of benserazide is absorbed via oral administration. Following an oral dose of benserazide maximal plasma concentrations occur at approximately 1 hours.

Levodopa
Absorption: Following an oral dose of levodopa maximal plasma concentrations occur at approximately 1-2 hours.

Concomitant food intake decreases the C_{max} and AUC by 30 and 15 %, respectively.

Study LEBE-DEV-T0216/1229
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Levodopa/Benserazide, 200 mg/50 mg, tablets with Madopar, 200 mg/50 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of levodopa were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2016-08-11 and 2016-10-27.

Results
The applicant states that due to limited bioavailability and chemical instability of benserazide, the levels of benserazide were not detectable, so only levodopa was used as the bioequivalent determinant.

The results from the pharmacokinetic and statistical analysis for levodopa are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for levodopa, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**4046.5 ± 1265.48**	**2415.023 ± 999.97**	**0.66 (0.33-3.50)**
Reference	**3996.5 ± 1173.22**	**2352.635 ± 985.72**	**0.83 (0.50-3.00)**
***Ratio (90% CI)**	**100.79 (97.11-104.61)**	**103.11 (89.40-118.93)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For levodopa, 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 %.

A biowaiver was sought for the strength of 100 mg/25 mg.

Discussion and overall conclusion
Based on following, it is sufficient to determine bioequivalence only based on levodopa:

a) There is a difficulty in measuring benserazide in reliable way.
b) Benserazide is a peripheral decarboxylase inhibitor and does not have direct therapeutic effect.
c) As the extracerebral decarboxylase is not yet completely inhibited, even at very high concentrations of benserazide, a difference of benserazide absorption should be seen on levodopa concentrations.

The bioequivalence study 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.

Absence of studies with the additional strength of 100 mg/25 mg is acceptable.

Based on the submitted bioequivalence study, Levodopa/Benserazide is considered bioequivalent with Madopar.

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 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 Levodopa/Benserazide Owlpharma.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
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 Risk Management Plan, version 1.0 signed 22.09.2020 is considered acceptable.

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 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Carbidopa/Levodopa Fair-Med (SE/H/1413/001-004/DC) concering content and Morfin Owlpharma (d.sp.nr: 31455) concerning layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Levodopa/Benserazide Owlpharma is found adequate. There are no objections to approval of Levodopa/Benserazide Owlpharma, 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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Levodopa/Benserazide Owlpharma, 100 mg/25 mg, Tablet was positively finalised on 2021-10-06.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se