COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Carneus 1 g/10 ml oral solution

# (levocarnitine)

# NL/H/4944/001/DC

# Date: 12 April 2021

**This module reflects the scientific discussion for the approval of Carneus 1 g/10 ml oral solution. The procedure was finalised at 17 December 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
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| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Carneus 1 g/10 ml oral solution, from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

The product is indicated for the treatment of primary (systemic) carnitine deficiency.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Carnitene, 100 mg/ml oral solution which has been registered in The Netherlands by Alfasigma Nederland B.V. since 3 February 1986.

The concerned member state (CMS) involved in this procedure was France.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Carneus is a clear, colourless to slightly yellow solution with an odour of orange. Each 10 ml contains 1 g levocarnitine (100 mg/ml).

The oral solution is packed in amber coloured glass single dose vials of 10 ml nominal content each, with a LDPE cap.

The excipients are malic acid (E296), sodium benzoate (E211), saccharin sodium (E954), orange flavour (containing flavouring substances, natural flavouring substances, flavouring preparations, propane 1, 2 – diol), sodium hydroxide (for pH adjustment) (E524) and water purified.

## II.2 Drug Substance

The active substance is levocarnitine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder or colourless crystals and hygroscopic. The substance is freely soluble in water, soluble in warm ethanol 96%, practically insoluble in acetone. It is stated by active substance manufacturer that only one polymorphic form exists. As the finished product is a

water based oral solution and the active substance is diluted in water during manufacturing process, polymorphism is not relevant for particular dosage form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process is described in the ASMF and is divided into three stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for control of residual solvents and microbiological purity. Batch analytical data demonstrating compliance with this specification have been provided for several batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Reference is made to the ASMF.

## II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The use and quantity of antimicrobial preservative is justified. The choices of the packaging and manufacturing process are justified since are common for particular dosage form. Similarity with originator product is demonstrated from quality point of view by comparing three batches of generic and originator product. The pharmaceutical development of the product has generally been adequately performed

Manufacturing process
The manufacturing process of levocarnitine oral solution involves complete dilution of active substance and excipients in purified water before mixing all together followed by filtration and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. requirements. Orange flavour complies with the in-house specification and stricter limit for conductivity is set for water used in manufacturing process. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity (active substance, preservative), deliverable volume, density, pH, uniformity of dosage units, assay, assay of preservative, related substances, microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from four-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for four full-scaled batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended packaging. At all conditions all the tested parameters were well within the specifications. The photostability study is included in the stability data. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'This medicinal product does not require any special temperature storage conditions. Keep the vials in the outer carton in order to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Carneus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

# III. NON-CLINICAL ASPECTS

## III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Carneus is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

## III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Carnitene which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Levocarnitine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

## IV.2 Pharmacokinetics

Biowaiver

An exemption from the requirement to bioequivalence/therapeutic equivalence/ comparative bioavailability study has been requested with a detailed biowaiver justification, attempting to demonstrate that the requirements for *in vivo* demonstration of bioequivalence between the two medicinal products can be waived.

Carneus 1 g/10 ml oral solution with the active substance levocarnitine can be considered a BCS Class III drug. This application is for an oral solution and reference is made to a reference oral solution. For oral solutions Appendix II of the Bioequivalence guideline is applicable. Additionally, also the EMA's Question and Answer document 6.3 *clarification on how to apply the reference made in Appendix II of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1404/98 Rev.1/Corr**)* is applicable, which indicates that for comparison of excipients the BCS classification should be taken into account.

The MAH provided test results showing that also the reference product contains comparable amounts of sodium saccharine. Overall, the composition of Carneus, compared to the reference product, is, except for flavouring agent, quantitatively very similar. In addition, similar results were found for appearance, related substances, assay of active substance, deliverable volume, relative density, pH value and microbiological attributes.
Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

### 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 Carneus.

**Table 1. Summary table of safety concerns as approved in RMP**

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| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Carnitene. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Carneus 1 g/10 ml oral solution has a proven chemical-pharmaceutical quality and is a generic form of Carnitene, 100 mg/ml oral solution. Carnitene is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Carneus with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 December 2020.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
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