Leovascarnitine 30% Paediatric Oral Solution

(Leovascarnitine)

PL 08381/0009

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 10
Summary of Product Characteristics Page 11
Patient Information Leaflet Page 12
Labelling Page 13
Levocarnitine 30% Paediatric Oral Solution

PL 08381/0009

LAY SUMMARY

On 30th July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Sigma-Tau Industrie Farmaceutiche Riunite SpA, a Marketing Authorisation (licence) for the medicinal product Levocarnitine 30% Paediatric Oral Solution (PL 08381/0009). This medicine is only available on prescription from the doctor.

Levocarnitine paediatric contains synthetic levocarnitine. Levocarnitine is, in nature, a component of the cell where it plays an essential role in energy production and transport. It is used to treat primary and secondary carnitine deficiency in children under 12 years of age, infants and newborns.

Carnitine deficiency occurs when the body has a shortage of levocarnitine. Levocarnitine paediatric makes up for the body’s lack of levocarnitine and helps give the body more energy.

No new or unexpected safety concerns arose from this application and it was therefore, judged that the benefits of taking Levocarnitine 30% Paediatric Oral Solution outweigh the risks, hence a Marketing Authorisation has been granted.
Levcarnitine 30% Paediatric Oral Solution

PL 08381/0009

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .................................................. Page 4
Pharmaceutical assessment ............................... Page 5
Non-clinical assessment ..................................... Page 7
Clinical assessment ......................................... Page 8
Overall conclusion and benefit-risk assessment .... Page 9
INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Levocarnitine 30% Paediatric Oral Solution (PL 08381/0009) on 30th July 2013. This prescription only medicine (POM) is used in the treatment of primary and secondary carnitine deficiency in children under 12 years, infants, and newborns.

This is a national abridged application for Levocarnitine 30% Paediatric Oral Solution submitted under Article 10c of Directive 2001/83/EC, as amended. This application cross-refers to Carnitor 30% Paediatric oral solution (PL 08381/0005), authorised to Sigma-Tau Industrie Farmaceutiche Riunite SPA on 2nd November 1992.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

A summary of pharmacovigilance system (PMFS) and detailed Risk Management Plan (RMP) have been provided with this application and these are satisfactory.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE**

**Nomenclature**

rINN: Levocarnitine

**Chemical Names:** 
(R)-3-Carboxy-2-hydroxy-\(N,N,N\)-trimethyl-1-propanaminium hydroxide, inner salt. 
(R)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt [541-15-I].

**Structure:** 

![Structure](image)

Molecular Formula: \(C_7H_{15}NO_3\)

Molecular Weight: 161.20 g/mol

Appearance: A white or almost white, crystalline powder.

Solubility: The substance is freely soluble in water.

Levocarnitine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance levocarnitine are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of the pharmaceutical excipients sorbitol solution (70%) (E420), tartaric acid (E334), sodium propyl hydroxybenzoate (E217), sodium methyl hydroxybenzoate (E219), colourless cherry flavour, colourless sour black cherry flavour and saccharose.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of colourless cherry flavour and colourless sour black cherry flavour which are covered by an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that none of the excipients are of animal or human origin.

**Pharmaceutical development**

Suitable pharmaceutical development data have been provided for this application.
Manufacture
The proposed manufacturing process is consistent with the details registered for the referenced product and the maximum full scale batch size is stated.

Finished product specification
The proposed finished product and shelf-life specification are in line with the details registered for the referenced product.

Container Closure System
The product is supplied in amber glass bottles with a polyethylene lined, polypropylene child proof cap. Bottles contain a nominal volume of 20 ml of product.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with storage conditions “Store below 25°C” and “Keep bottle in the outer carton in order to protect from light and moisture” have been set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Carnitor 30% Paediatric oral solution (PL 08381/0005). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification of the rationale for bridging is accepted

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report/Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of levocarnitine are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

Suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.
**CLINICAL ASSESSMENT**

**Clinical Pharmacology**
The clinical pharmacology of levocarnitine is well known.

As per guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*), a bioequivalence study is not required if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution. Bioequivalence studies may be waived if the excipients contained in the product do not affect gastrointestinal transit, absorption, solubility or *in-vivo* stability of the active substance. These criteria are fulfilled. Therefore, no biostudies are provided by the applicant and none are required.

**Clinical efficacy**
No new efficacy data have been submitted and none are required for applications of this type.

**Clinical safety**
No new safety data were supplied or required for this application.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPC, PIL and labelling are medically satisfactory.

**Clinical Expert Report**
The clinical overview is written by an appropriately qualified physician and consists of a review of the published literature.

**Marketing Authorisation Application (MAA) Form**
The MAA form is medically satisfactory.

**Clinical Conclusion**
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Levocarnitine 30% Paediatric Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new efficacy data were submitted and none are required for applications of this type.

The safety profile of levocarnitine is well-known. No new or unexpected safety issues or concerns have been identified for this product.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Levocarnitine is a well known active substance. Extensive clinical experience with levocarnitine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 10(^{th}) January 2013.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 19(^{th}) February 2013.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 14(^{th}) May 2013 and 17(^{th}) June 2013.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 7(^{th}) June 2013 and 5(^{th}) July 2013.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 30(^{th}) July 2013.</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
UKPAR Levocarnitine 30% Paediatric Oral Solution
PL 08381/0009

LABELLING

For oral use only.

Use as directed by your doctor

Read the package leaflet before use.

Store below 25°C.

Keep in the original packaging in order to protect from light and moisture.

Keep out of the reach and sight of children.

POM

Solution containing Levocarnitine 300 mg/1 ml.

Also contains Sorbitol Solution (E420) and Sucrose and Sodium Propyl Hydroxypropiolactone (E121) and Sodium Methyl Hydroxypropionate (E219) as preservatives.