IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Magnesium Kora Healthcare 97 mg tablets
Magnesium
PA1748/004/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Magnesium Kora Healthcare 97 mg tablets, from Kora Corporation Ltd on 26th March 2020
in the treatment and prevention of magnesium deficiency in adults, adolescents and children aged from 12 years.

This application concerns an Article 10a of Directive 2001/83/EC, "well established use" for a Marketing Authorisation Application (MAA) for a magnesium citrate tablet with 97.2 mg of magnesium citrate nonahydrate (MgCN) as the active ingredient, which equates to 4mmol of elemental magnesium

Given the status of well-established use, the applicant has not undertaken any new clinical trials with the Magnesium Kora Healthcare 97 mg tablets and this is therefore a bibliographic application based on a comprehensive search of the published literature.

This is a Decentralised Procedure, with IE as the Reference Member State (RMS) and BE, NL and the UK(NI) as the Concerned Member States (CMSs).

This product is subject to prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Magnesium Kora Healthcare 97 mg tablets
Name(s) of the active substance(s) (INN)	Magnesium citrate nonahydrate
Pharmacotherapeutic classification (ATC code)	A12CC04 Magnesium citrate
Pharmaceutical form and strength(s)	Tablet; 97 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1748/004/001
Marketing Authorisation Holder	Kora Corporation Ltd t/a Kora Healthcare
MRP/DCP No.	IE/H/1105/001/DC
Reference Member State	IE
Concerned Member State	BE NL UK (NI)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Magnesium Kora Healthcare 97 mg tablets.

II.2 Drug substance

The active substance is magnesium citrate nonahydrate, an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. specifications.

P.5 Control of Finished Product

The finished product specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Magnesium Kora Healthcare 97 mg tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Magnesium Citrate Nonahydrate is a widely used and well-known active substance and the pharmacodynamic, pharmacokinetic and toxicological properties of magnesium citrate nonahydrate are well-known. No new preclinical data have been submitted. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate for this well-established use application and no new data were found that would alter the risk-benefit balance for magnesium citrate nonahydrate.

III.2 Ecotoxicity/environmental risk assessment

Magnesium Citrate Nonahydrate is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Magnesium citrate nonahydrate is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As Magnesium Citrate Nonahydrate is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Magnesium Citrate Nonahydrate is a widely used and well-known active substance and the pharmacodynamic, pharmacokinetic of magnesium citrate nonahydrate are well-known. A comprehensive clinical overview has been submitted by the applicant. Given the status of well-established use, the applicant has not undertaken any new clinical trials with the Magnesium Kora Healthcare 97 mg tablets formulation, and this is therefore a bibliographic application based on a comprehensive search of the published literature.

The use of magnesium citrate and other salts of magnesium in treating magnesium deficiency is well established, and the published data have adequately described the properties of these salts.

It has been demonstrated that the product or an equivalent product(s) has been in medicinal use for the proposed indication for at least 10 years with an acceptable level of efficacy and safety. Formal indications of prevention and treatment are currently approved for a number of European licensed magnesium products.

The intended patient populations are adults, adolescents and children from 12 years .

The recommended daily dose for an adult (> 18 years) is 12-24 mmol magnesium, e.g. 1 – 2 tablets administered 3 times a day (equivalent to 291.6– 583.2 mg magnesium or 12-24 mmol magnesium daily).

The recommended daily dose for children (12 to 18 years) and adolescents is 12 mmol magnesium, e.g. 1 tablet administered 3 times a day (equivalent to 291.6 mg magnesium or 12 mmol magnesium daily).

The approved indication is for *the treatment and prevention of magnesium deficiency in adults, adolescents and children aged from 12 years*.

The intended posology for Magnesium Kora Healthcare 97 mg tablets is 291.6 to 583.2mg magnesium (12-24mmol) per day.

IV.2 Pharmacokinetics

The use of magnesium citrate and other salts of magnesium in treating magnesium deficiency is well established, and the published data have adequately described the absorption, pharmacokinetic and pharmaocdymanic performance of those salts. The submitted overview based on literature review is appropriate.

The results of a dissolution test for the MagnaCitrate 97mg Tablets in HCl meets the requirements for a high solubility compound in accordance with EMA Guidance.

Variability is apparent in the absorption between subjects, and between different magnesium salts, this is not necessarily of clinical significance when the dosing period is sufficiently long however caution should be exercised when switching between magnesium preparations.

IV.3 Pharmacodynamics

No pharmacodynamic or therapeutic action is being claimed for the applicant's product other than the restoration and maintenance of normal magnesium levels in the body.

Magnesium acts through a variety of mechanisms, primarily through its interaction with different kinase enzyme pathways and as an antagonist to calcium ions.
There is no specific target tissue for magnesium. Magnesium is a predominantly intracellular ion and is distributed between the nucleus, endoplasmic or sarcoplasmic reticulum, mitochondria, and cytoplasm (Romani 2017).
The submitted overview based on a literature review is appropriate.

IV.4 Clinical Efficacy
The applicant has provided evidence from several sources to support the efficacy of Magnesium Kora Healthcare 97 mg tablets in the proposed indication**:** these include clinical studies on the treatment of magnesium deficiency in various disease conditions.

This data included 4 meta-analyses two of which are regarded as the pivotal studies in this bibliographic application (Witkowski 2011, Zhang 2016a); with the interventional studies providing additional support and expanding the patient population base. The evidence provided for magnesium salts other than the citrate salts are applicable and can be considered supportive based on the data provided by the applicant.

The efficacy of Magnesium Kora Healthcare 97 mg tablets for use in under 12 years of age was not assessed as part of this application. In common with a significant proportion of medicines which are used in children, there are limited published data to demonstrate the efficacy of the medicine in this age group, however the applicant has provided sufficient evidence to support the efficacy in children and adolescents from 12 years of age.

IV.5 Clinical Safety

Magnesium Kora Healthcare 97 mg tablets have an established favourable safety profile based on the bibliographic evidence provided by the applicant including tabulated safety results.

Clinical studies have confirmed the safe and effective use of magnesium citrate within a wide range of patient groups, and the safety profile is supported by extensive post-marketing
experience with similar products.

The most common adverse event in all magnesium salts is a mild laxative effect that is dose dependent and at higher doses may lead to diarrhoea. These effects normally quickly resolve on reduction or cessation of the dose.

The safety of Magnesium Kora Healthcare 97 mg tablets for use in under 12 years of age was not assessed as part of this application.In common with a significant proportion of medicines which are used in children, there are limited published data to demonstrate the safety of the medicine in this age group, however the applicant has provided sufficient evidence to support the safety in children and adolescents from 12 years of age.

For full safety prescribing information for Magnesium Kora Healthcare 97 mg tablets, please see the Summary of Product Characteristics (SmPC).

Risk Management Plan (RMP)
The applicant 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 Magnesium Kora Healthcare 97 mg tablets

The revised RMP (version 0.3, dated 02/11/2020) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Periodic Safety Update Report (PSUR)
The medicinal product is authorised under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC. No routine PSURs need to be submitted unless it is stated as a condition in the marketing authorisation. Marketing authorisation holders

shall continuously check the European medicines web-portal to see if the active substance has been included in the list of Union reference dates (EURD list). If yes, the PSURs shall be submitted in accordance with the requirements set out in the EURD list.

IV.6 Discussion on the clinical aspects

This application is submitted based upon Article 10a of Directive 2001/83/EC. The bibliographic application demonstrates that magnesium citrate nonahydrate (MgCN) has a well-established use, with an acceptable level of safety and efficacy, as outlined in Part II.1 of Annex I to Directive 2001/83/EC.

One dissolution study has been conducted.

The applicant has provided evidence from several sources to support the efficacy of magnesium citrate in the proposed indication**:** these include the bioavailability, pharmacokinetic studies and clinical studies on the treatment of magnesium deficiency in various disease conditions. This data included 4 meta-analyses two of which are regarded as the pivotal studies in this bibliographic application (Witkowski 2011, Zhang 2016a); with the interventional studies providing additional support and expanding the patient population base.

It has been demonstrated that the product or an equivalent product(s) has been in medicinal use for the proposed indication for at least 10 years with an acceptable level of efficacy and safety. Formal indications of prevention and treatment are currently approved for a number of European licensed magnesium products.

V. OVERALL CONCLUSIONS

This application concerns an Article 10a of Directive 2001/83/EC, "well established use" for a Marketing Authorisation Application (MAA) for a magnesium citrate tablet.

Given the status of well-established use, the applicant has not undertaken any new clinical trials with the Magnesium Kora Healthcare 97 mg tablets, and this is therefore a bibliographic application based on a comprehensive search of the published literature

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Magnesium Kora Healthcare 97 mg tablets has a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable

VI. REVISION DATE

22.1.2026

VII. UPDATES