IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Magnaspartate 243 mg powder for oral solution
Magnesium aspartate dihydrate
PA1748/002/001

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 quality, safety and efficacy data, the Member States have granted a marketing authorisation for Magnaspartate 243mg Powder for Oral Solution from Kora Corporation Limited T/A Kora Healthcare on 15th May 2015.

The product is indicated for Treatment and prevention of magnesium deficiency, as diagnosed by a doctor. Magnaspartate is indicated in adults, children and adolescents aged from 2 years.
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, "well established use".

Magnaspartate is an organic salt of magnesium, and has been used in the past as a food supplement in the treatment and prevention of magnesium deficiency. Various salts of magnesium, both organic and inorganic have been used for this purpose over several years, and have been regulated as food supplements under the applicable National and European regulations.

Magnesium acts through a variety of mechanisms, primarily through its interaction with different kinase enzyme pathways and as an antagonist to calcium ions.

II. QUALITY ASPECTS

11.1 Introduction

The product Magnaspartate 243mg Powder for Oral Solution contains Magnesium aspartate dihydrate as the active substance. It also contains Sucrose, Citric acid monohydrate, Peach/apricot flavour, Saccharin sodium and Silica, colloidal anhydrous. It is packaged in single dose sachets made of Laminated foil (Paper/Aluminium/Polyethylene). Each pack contains 10 or 20 sachets.

11.2 2.2 Drug Substance

The active substance is Magnesium aspartate dihydrate, an established active substance monographed in European Pharmacopoeia, monograph number **1445.** It is manufactured in accordance with Good Manufacturing Practice (GMP). EDQM Certificate of suitability (CEP) procedure is used. The manufacturer of the drug substance Magnesium aspartate dihydrate has obtained a certificate of suitability and the CEP is presented in the documentation.

The active substance specification is considered adequate to control the quality and meets the current requirements of the monograph in the Ph. Eur. For Magnesium aspartate dihydrate. Batch analytical data demonstrating compliance with this specification have been provided.

No materials of animal origin are used in the manufacture of the drug substance.

Appropriate stability data have been provided.

11.3 Medicinal Product

II.3..1 Composition

Magnaspartate 243mg Powder for Oral Solution is a white powder with a peach/apricot-like flavour presented in single sachets. Each sachet contains magnesium aspartate dihydrate equivalent to 243 mg of magnesium.
The other excipients in the product are Sucrose, Citric acid monohydrate, Peach/apricot flavour, Saccharin sodium and Silica, colloidal anhydrous.

II.3.2 Pharmaceutical Development

The pharmaceutical development is adequately described in accordance with the relevant European guidelines. Use of the excipients is justified.

II.3.3 Manufacture

A description and flow-chart of the manufacturing method has been provided and is satisfactory.

In-process controls are appropriate considering the nature of the product and the method of manufacture. The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing site.
The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

II.3.4 Control of Other Substances (Excipients*/Ancillary Substances)*
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product.

II.3.5 Control of Finished Product
The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the Ph. Eur. requirements for "Powders and granules for oral solutions and suspensions" and the standard requirements associated with powders for solutions for oral use. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory description and validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material
The product is packaged in Laminated foil (Paper/Aluminium/Polyethylene) single dose sachets. Satisfactory specifications and certificates of analysis have been provided for all packaging components. Primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 10 and 20 sachets.

II.3.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC).

Details of in-use shelf life of the product (once reconstituted) is stated in the Summary of Product Characteristics (SPC) . The sachet can be reconstituted in water, orange juice or tea. If necessary, Magnaspartate in 200ml water can be administered via a gastric, duodenal, and nasal feeding tube. Details of reconstitution and a method of administration are stated in the Summary of Product Characteristics (SPC).

II.4 Discussion on chemical, pharmaceutical and biological 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 Magnaspartate 243mg Powder for Oral Solution.

III. NON-CLINICAL ASPECTS

The applicant has presented literature-based evidence demonstrating the non-clinical profile of this product. Magnesium-based food supplements and medicinal product have been in use for several years, and the positive non-clinical profile is supported by clinical evidence.

III. 5 Environmental Risk Assessment (ERA)
Since Magnaspartate 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.

IV. CLINICAL ASPECTS

Pharmacokinetics
The applicant has presented several publications demonstrating the pharmacokinetic profile of magnesium aspartate dihydrate.

Organic-based magnesium salts have a higher solubility and therefore a faster absorption and higher bioavailability than inorganic salts. Magnesium is widely distributed in the body, with the bony skeleton acting as a reservoir. Magnesium is not metabolised in the body, whereas aspartate is metabolised to other amino acids in the liver.

There are no specific dose recommendations in special populations, save patients with severe renal impairment. Magnesium is primarily excreted by the kidneys, which is significantly reduced in patients with severe renal impairment.
Magnesium-containing supplements are therefore contraindicated in patients with severe renal impairment, and should be used with caution in patients with mild to moderate impairment. There is no dose adjustment necessary in patients with mild to moderate renal impairment.

There is no evidence of an adverse benefit risk profile with regards to the use of this substance in pregnant women or nursing mothers.

Pharmacodynamics
Magnesium exerts its effects through its actions on various kinase enzymes, and through its action as a calcium antagonist. Whereas symptomatic hypomagnesaemia is usually treated with parenteral magnesium supplements, asymptomatic hypomagnesaemia can be appropriately treated using enteral forms.

The applicant has provided evidence suggesting that enteral supplementation is more efficacious to parenteral supplementation in asymptomatic patients, due to the slower increase in systemic magnesium levels, thus reducing the compensatory rise in excretion.

Clinical efficacy
The clinical efficacy of magnesium supplementation in adults and children over 2 years for the treatment and prevention of magnesium deficiency is well established, based on the bibliographic evidence provided by the applicant.
Regarding the paediatric posology, the applicant has conducted a study to investigate the use of a CE marked 5mL spoon for the measurement of an appropriate dose for the paediatric subset between 2 and 10 years. Based on the results of this study, it is acceptable that such a CE marked device could be used to safely determine the dose in this cohort.

Clinical safety
Magnesium has a favourable safety profile in adults and children above 2 years of age, based on the bibliographic evidence provided by the applicant.

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 Magnaspartate.

- Pharmacovigilance plan: Routine pharmacovigilance activities are considered sufficient for monitoring of the safety concerns.
- There are no additional risk minimisation measures proposed or required. Routine risk minimisation measures are considered sufficient.
- Risk minimisation plan: Routine risk minimisation measures include reference to SmPC and PIL wording. These are outlined for each risk.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity to the active substance or to any of the excipients. • Gastrointestinal disorders in patients with rare hereditary problems of fructose intolerance OR patients with glucose-galactose malabsorption OR patients with sucrase-isomaltase insufficiency.

	• Overdose toxicity in patients with severe renal impairment (glomerular filtration rate < 30 ml/min) • Cardiac conduction disorders in patients with existing disorders of cardiac conduction (bradycardia). Because of increased magnesium losses, a dose adjustment of magnesium may be necessary when taking: Aminoglycoside antibiotics, cisplatinum and cyclosporin A. Diuretics (such as thiazide and furosemide). EGF-receptor antagonists (such as cetuximab and erlotinib). Proton pump inhibitors (such as omeprazole and pantoprazole). Viral DNA polymerases-inhibiting foscarnet, pentamidine, rapamycin and amphotericin B. • Reduced efficacy related to interaction with other medicinal products Cellulose sodium phosphate; edentate disodium; Fluorides and tetracycline; Aminoquinolines, quinidine and quinidine derivatives nitrofurantoin, penicillamine, iron, bisphosphonates, eltrombopag, nitroxoline
Important potential risks	None
Missing information	None

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Hypersensitivity to the active substance or to any of the excipients	SPC and PIL information	None
Gastrointestinal disorders in patients with rare hereditary problems of fructose intolerance OR patients with glucose-galactose malabsorption OR patients with sucrase-isomaltase insufficiency	SPC and PIL information	None
Overdose toxicity in patients with severe renal impairment (glomerular filtration rate < 30 ml/min)	SPC and PIL information	None
Cardiac conduction disorders in patients with existing disorders of cardiac conduction (bradycardia).	SPC and PIL information	None
Reduced efficacy when given with specific medications	SPC and PIL information	None
Reduced efficacy related to interaction	SPC and PIL information	None

with other medicinal products		

IV. 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.

V. OVERALL CONCLUSIONS

Overall, the benefit risk profile of this product is positive for adult and paediatric patients over the age of 2 years.