Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Magmedi 97 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains magnesium citrate nonahydrate equivalent to 97.2 mg (4 mmol) of magnesium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, oblong tablet, marked with "Mg" and "97" on either side of a score line on one side. Dimensions: 18 mm x 8.7 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Magmedi is indicated for the treatment and prevention of magnesium deficiency in adults, adolescents and children aged from 12 years.

4.2 Posology and method of administration

The duration of magnesium treatment required will depend on the clinical circumstances of each patient
It is recommended that serum magnesium levels should be monitored at regular intervals e.g. every 3-6 months, particularly in children and in patients with renal impairment.
Posology
Adults (> 18 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).

Children and adolescents (12 to 18 years)
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).

Special populations

Children less than 12 years:
Magmedi is not recommended for children less than 12 years as
the safety and efficacy of Magmedi in children less than 12 years has not yet been established.
Other pharmaceutical forms/strengths may be more appropriate for administration to
this population.

Elderly:
As older patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal impairment below).
Patients who experience difficulties swallowing tablets should preferably be treated with a magnesium powder for oral solution.

Patients with renal impairment:
Magmedi is contraindicated in patients with severe renal impairment (see section 4.3).
There is no dose adjustment necessary in patients with mild to moderate renal impairment.

Method of administration

For oral use.
The tablet may be broken in half using the score line. The score line is present only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe renal impairment (glomerular filtration rate < 30 ml/min).

4.4 Special warnings and precautions for use

If an undesirable effect occurs, such as diarrhoea, the therapy should be temporarily interrupted and can be restarted after improvement and /or elimination of the symptoms with a reduced dosage.

In the case of confirmed magnesium deficiency, concomitant hypocalcaemia and hypokalaemia should be suspected and corrected if confirmed since magnesium deficiency is frequently secondary to those conditions.

Exercise caution when prescribing Magmedi for patients with disorders of cardiac conduction.

Magmedi is not intended as first-line treatment for patients with severe symptomatic hypomagnesemia or serum levels <0.4mmol/L for whom intravenous magnesium is indicated. Subject to local treatment protocols, oral magnesium treatment may begin when serum magnesium rises above 0.4 mmol/L or when acute symptoms of hypomagnesemia have resolved.

The bioavailability of magnesium preparations can vary, therefore caution should be exercised when switching between magnesium preparations to ensure tolerability and equivalent therapeutic effect.

Diabetes mellitus is commonly associated with magnesium depletion. Other associated endocrine conditions that may be linked to hypomagnesaemia, include hyperthyroidism and hyperaldosteronism, these conditions should be considered, and excluded.

4.5 Interaction with other medicinal products and other forms of interactions

As magnesium and other medicinal products may mutually influence each other's absorption, a time interval of 2 to 3 hours should generally be respected if possible.

This specifically applies to:

- ***Cellulose sodium phosphate; edetate disodium****:* concurrent use with magnesium supplements may result in binding of magnesium; patients should be advised not to take magnesium supplements within 1 hour of cellulose sodium phosphate or edetate disodium.

- ***Fluorides and tetracycline****:* if they must be used, the doses must be separated by 2 to 3 hours or more to prevent their admixture in the gut.

- ***Aminoquinolines, quinidine and quinidine derivatives, nitrofurantoin, penicillamine, iron, bisphosphonates, eltrombopag, nitroxoline:*** to avoid impairment of absorption, magnesium preparations should be taken 3 to 4 hours before or after the administration of those drugs.

Magnesium homeostasis influenced by medication
Because of increased magnesium losses, a dose adjustment of magnesium may be necessary when taking the following substances:

Diuretics (e.g. thiazide, furosemide) are widely used in the treatment of hypertension, heart failure and kidney diseases. They increase urinary output with hypermagnesuria probably leading to hypomagnesaemia and magnesium depletion.

EGF-receptor antagonist (e.g. cetuximab, erlotinib, panitumumab). Since EGF is a magnesiotropic hormone, treatment with EGF-receptor antagonists can result in severe hypomagnesaemia.

VEGF-blockers Bevacizumab is a humanised IgG1 antibody that binds and inhibits VEGF activity. Hypomagnesaemia is recognised as a very common adverse reaction associated with bevacizumab therapy.

PD-1 inhibitors Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody that works as a checkpoint inhibitor that allows the immune system to kill cancer cells. Treatment with nivolumab can result in dysregulation of magnesium metabolism.

Long-term treatment with proton pump inhibitors (e.g. omeprazole, esomeprazole, lansoprazole and pantoprazole) has been related to severe hypomagnesaemia, probably due to disturbances in absorption.

Aminoglycoside antibiotics (e.g. gentamycin, tobramycin and amikacin) are widely used in the treatment of severe bacterial infections. Studies showed that in 25 % of the patients, hypomagnesaemia occurs due to renal magnesium loss.

Foscarnet is a pyrophosphate analogue that inhibits many viral DNA polymerases.
Hypomagnesaemia is among others a side effect of foscarnet treatment as foscarnet is a potent chelator of divalent cations. Other viral DNA polymerase inhibitors include Pentamidine, Rapamycin and Amphotericin B.

Immunosuppressive agents (e.g. Ciclosporin A and Tacrolimus) increase the loss of magnesium via the kidneys.

Chemotherapy agents (e.g. Cisplatin and Carboplatin) can result in hypomagnesemia - a widely recognised toxic side effect of chemotherapy and occurs due to renal tubular toxicity.

Magnesium homeostasis influenced by medical conditions
Excessive excretion of magnesium into the urine is a cause of magnesium depletion. Osmotic diuresis due to glucosuria can result in magnesium depletion, therefore, those with diabetes mellitus have an increased requirement for magnesium.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women over 16 weeks' gestation (more than 1,000 pregnancy outcomes) do not indicate malformative toxicity or feto/neonatal toxicity of magnesium.
Magmedi can be used during pregnancy if clinically needed.

Administration of aminoglycoside antibiotics should be avoided during this period, as there are indications of interactions (see 4.5).

Lactation
Magmedi can be used during breast-feeding. Magnesium citrate / metabolites are excreted in human milk, but at therapeutic doses of Magmedi no effects on the breastfed newborns/infants are anticipated.

Fertility
Based on long-term experience, no effects of magnesium on male and female fertility are anticipated.

4.7 Effects on ability to drive and use machines

Magmedi has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

At high dosage diarrhoea or gastrointestinal irritation may occur. If diarrhoea occurs, the daily dose should be reduced and gradually increased later if needed.

In cases of high doses and long-term use fatigue may be experienced. This may be an indication that an elevated magnesium level has been achieved. Hypermagnesemia is rare after oral administration of magnesium salts, unless there is renal dysfunction.

The evaluation of undesirable effects is based on the following frequencies:
Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);

Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

Safety information is based on pooled data from clinical trials on magnesium supplementation.

MedDRA System Organ Class	Frequency	Undesirable Effects
Gastrointestinal disorders	Common	Soft stools or diarrhoea following high dosage
General disorders and administration site conditions	Very rare	Fatigue if used long-term

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

In the case of intact renal function, magnesium intoxication due to oral overdose of magnesium is not expected. Only in the case of severe renal insufficiency accumulation of magnesium may arise in combination with a manifested intoxication.

In general, plasma concentrations up to 2 mmol/l magnesium are well tolerated.

Intoxication symptoms:
Blood pressure fall, nausea, vomiting, hyporeflexia, somnolence, changes in the electrocardiogram, respiratory depression and cardiac arrest.

Intoxication therapy:
Intravenous administration of calcium and slow intravenous administration of neostigmine methylsulfate;
Intravenous and per-oral administration of isotonic sodium chloride solution; ventilatory and circulatory support;
When patients have renal insufficiency haemodialysis may be used to lower the serum magnesium concentration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mineral Supplements, magnesium citrate; ATC code: A12CC04

Magnesium is a cofactor in >300 enzymatic reactions. It acts as an essential co-factor for all ATP-binding enzymes.

Magnesium plays an important role in cellular electrolyte homeostasis and in the neuromuscular membrane stabilization.

Magnesium is associated with the following:

- inhibition of neuromuscular transmission and stabilization of the phospholipids of the cell membrane
- magnesium acts as a physiological calcium antagonist and as such regulates the contractility of the heart and stabilises cardiac rhythm. Magnesium deficiency has been shown to result in cardiovascular disorders such as cardiac dysrhythmias, which may be manifested by a rapid heart rate (tachycardia), skipped heart beats (premature beats), or a totally irregular cardiac rhythm (fibrillation).
- a low magnesium status leads to arterial vasoconstriction and thrombocyte aggregation. Migraine patients often show low magnesium levels, therefore, magnesium deficiency seems to play a role in the pathogenesis of migraine.

5.2 Pharmacokinetic properties

Absorption
Intestinal absorption is not directly proportional to magnesium intake but is dependent mainly on magnesium status. The lower the magnesium level, the more magnesium is absorbed in the gut: thus, relative magnesium absorption is high when intake is low and vice versa.

Magnesium is slowly and incompletely absorbed – primarily in the small intestine. The non-absorbable portion can produce a laxative effect.

Peak serum levels are reached after 4 to 7 hours. At 6 hours, magnesium absorption is approximately 80% complete.

Distribution
Magnesium is the main intracellular divalent cation, and the normal adult human body content is around 22.6g. About 60% of the magnesium is present in bone, of which 30% is exchangeable and functions as a reservoir to stabilise the serum concentration. About 20% is in skeletal muscle, 19% in other soft tissues and less than 1% in the extracellular fluid.

After oral administration the distribution of magnesium within the body depends on the filling state of magnesium levels in each individual case. The classical method of determining bioavailability using plasma concentration curves cannot be applied to magnesium.

The concentration of magnesium in the blood serum is subject to variations during the day. Due to the equilibrium between magnesium concentration in the blood serum and the depot in the bones, no conclusions concerning the depot in the body can be drawn from the concentration of magnesium in the blood serum. Neuromuscular hyper-excitability can be an indicator of magnesium deficiency.

Biotransformation
The active substance magnesium citrate nonahydrate readily dissociates into magnesium and citrate ions in aqueous solutions. These components are natural constituents of the human body.

Elimination
Magnesium is excreted principally by the kidney by glomerular filtration. Under normal conditions 3 to 5% of the filtered ion (2 to 4 mM per day) is excreted in the urine. Renal magnesium excretion is increased during diuresis induced by glucose, ammonium chloride, furosemide, ethacrynic acid, and organic mercurials.

Linearity/non-linearity
Meta-analysis has shown that oral supplementation with magnesium salts increases the level of circulating (serum/plasma) and urinary magnesium in a clinically and statistically significant time and dose-dependent manner.

5.3 Preclinical safety data

Effects in non-clinical studies were only observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Copovidone
Cellulose, Microcrystalline (E460(i))
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Aluminium blisters

Pack size: 60 or 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Kora Corporation Ltd t/a Kora Healthcare
Swords Business Park
Swords
Co. Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1748/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th March 2021

10 DATE OF REVISION OF THE TEXT

October 2021