SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Magnaspartate 243 mg powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 6.5 g sachet of powder contains magnesium aspartate dihydrate equivalent to 243 mg (10 mmol) of magnesium.

Excipient(s) with known effect:

Each sachet contains 2.706g sucrose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution

White powder with a peach/apricot-like flavour.

4.2 Therapeutic indications

Magnaspartate is indicated for the treatment and prevention of magnesium deficiency in adults and children aged 2 years and above.

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)
1-2 sachets daily (243-486 mg magnesium or 10-20 mmol magnesium)

Children and adolescents: 10 to 18 years
One sachet daily (equal to 243 mg magnesium) dissolved in 50-200ml of water, tea, or orange juice.

Children: 4-10 years
One sachet daily (equal to 243 mg magnesium) dissolved in 50-200ml of water, tea, or orange juice. Alternatively, for a half dosage, use half the volume of 1 sachet dissolved in 50-200ml of water (equal to 121.5 mg magnesium).

Children: 2 to 4 years
Half the volume of 1 sachet dissolved in 50-200ml water (equal to 121.5 mg magnesium).

The safety and efficacy of Magnaspartate in children below 2 years has not been established.

Renal patients:
Magnaspartate 243 mg 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.

Elderly:
No dose adjustment is necessary.

Method of administration

For oral use after solution in water, tea or orange juice.

Magnaspartate can be dissolved in 50-200mL water, tea or orange juice.
Stir until the solution in water is cloudy to transparent. In orange juice or tea inactive particles will be visible. The solution should be taken immediately following reconstitution or within 24 hours when dissolved in bottled water and stored below 25°C.

Note
If necessary, Magnaspartate in 200ml water can be administered via a gastric, duodenal, and nasal feeding tube. This should be administered immediately following reconstitution or within 24 hours when dissolved in bottled water and stored below 25°C.

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)
- Disorders of Cardiac conduction (bradycardia)

4.4 Special warnings and precautions for use

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.

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

Excipients:
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
Contains 2.706 g of sucrose per sachet. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth.

This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

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 edentate 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.

Because of increased magnesium losses, a dose adjustment of magnesium may be necessary when taking the following substances:

- Aminoglycoside antibiotics, cisplatinum and ciclosporin A
- Diuretics (such as thiazide and furosemide),
- EGF-receptor antagonists (such as cetuximab and erlotinib),
- proton pump inhibitors (such as omeprazole and pantoprazole) and

- viral DNA polymerases-inhibiting foscarnet, pentamidine, rapamycin and amphotericin B

For further information on mechaninsms of drug interactions see section 5.2.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women over 16 weeks gestation (more than 1000 pregnancy outcomes) indicate no malformative nor feto/neonatal toxicity of magnesium.
Magnaspartate 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
Magnaspartate can be used during breast-feeding.
Magnesium aspartate/metabolites are excreted in human milk, but at therapeutic doses of Magnaspartate 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

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

4.8 Undesirable effects

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).

MedDRA System Organ Class	Frequency	Undesirable Effects
Gastrointestinal disorders	Uncommon	Soft stools or diarrhoea following high dosage
General disorders and	Very rare	fatigue if used long-term

administration site conditions		

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.

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

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

In general, plasma concentrations up to 2 mmol/l 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 0.5 – 2 mg neostigmine methylsulfate;
Intravenous and per-oral administration of isotonic sodium chloride solution; ventilatory and circulatory support;
In case of renal insufficiency: haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mineral Supplements, magnesium ATC code: A12CC05

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:
- acts as a physiological calcium antagonist and as such regulates the contractility of the heart and stabilises cardiac rhythm
- stabilizes the phospholipids of the cell membrane
- inhibits neuromuscular transmission

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 2-3 hours. At 6h, 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.

Elimination
Absorbed magnesium is practically only secreted via the kidney.

Magnesium homeostasis influenced by medication

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) are used in the treatment of metastatic colorectal cancer. As EGF is a magnesiotropic hormone, treatment with EGF-receptor antagonists was related to severe hypomagnesaemia.

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

Aminoglycoside antibiotics (e.g. gentamycin, tobramycin) 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.

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, and diabetes mellitus is probably the most common clinical disorder associated with magnesium depletion. Therefore, diabetics have an increased requirement for magnesium.

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. Magnesium supplementation was effective in migraine prophylaxis.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Citric acid monohydrate
Peach/apricot flavour
Saccharin sodium
Silica, colloidal anhydrous

6.2 Incompatibilities

Media to be used for reconstitution; see section 4.2.

6.3 Shelf life

3 years
Use immediately following reconstitution or within 24 hours when dissolved in bottled water and stored below 25°C.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Sachets laminate foil comprises paper/aluminium/polyethylene.
Pack sizes: 10 and 20 sachets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Use in the paediatric population.
No special requirements.Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 39972/0002

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