Q&A 111.5

**What oral magnesium preparations are available in the UK and which preparation is preferred for the treatment and prevention of hypomagnesaemia?**

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Date prepared: 8th April 2015

**Background**

Oral magnesium preparations may be given for the treatment of chronic hypomagnesaemia in doses adjusted according to individual requirements (1). In acute symptomatic hypomagnesaemia, rapid replacement therapy with intravenous magnesium salts may be necessary (1). It is important to review any drugs which may be causing hypomagnesaemia. The Medicines and Healthcare Products Regulatory Agency (MHRA) has drawn attention to an association between hypomagnesaemia and the use of proton pump inhibitors (PPIs) (2).

Magnesium-L-aspartate (Magnaspartate®) has recently been licensed in the UK for the treatment and prevention of magnesium deficiency and will be available from April 2015 (3). Prior to this there were no oral magnesium preparations licensed in the UK for this indication which resulted in the prescribing of a range of unlicensed preparations.

**Answer**

**Licensing status**

Magnesium-L-aspartate (Magnaspartate®) is the preferred choice for the treatment and prevention of magnesium deficiency when clinically appropriate as it is the only UK licensed oral magnesium preparation for these indications. MHRA guidance states “An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient. An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient” (4). The requirement for a “special need” relates to the special clinical needs of the patient, rather than cost, convenience or operational needs and must be determined by the prescriber. For example if a patient was to suffer from dose-limiting diarrhoea with magnesium-L-aspartate, it would be acceptable to try an alternative magnesium preparation. There are many other oral magnesium salts available, examples of which are given in Table 1. The majority of these are unlicensed products.

**Evidence**

At the time of writing no national guidelines or fully published studies comparing oral magnesium salts for the treatment or prevention of hypomagnesaemia which evaluated clinical outcomes were identified.

The British National Formulary states oral magnesium may be given by mouth in a dose of 24 mmol daily in divided doses to prevent the recurrence of hypomagnesaemia, but there is limited evidence of benefit (5). Magnesium-L-aspartate and magnesium glycerophosphate are included in the British National Formulary for Children as an option for hypomagnesaemia (6). The National Institute for Health and Clinical Excellence (NICE) summarised the published evidence for the use of magnesium glycerophosphate to prevent recurrence of symptomatic hypomagnesaemia in people who have already been treated for this condition, generally by intravenous infusion. No clinical trials were found. Only three case reports for this indication in adults were found, in which oral magnesium glycerophosphate was not sufficient to maintain normal magnesium levels. No evidence for this indication in children was found (7). These are discussed in more detail below.
Bioavailability studies in healthy volunteers

There are several small studies which have compared the bioavailability of various magnesium preparations. However, these studies did not look at clinical outcomes in patients with hypomagnesaemia and were conducted in healthy volunteers.

A small study in 16 healthy volunteers compared four oral magnesium salts and concluded there is a relatively poor bioavailability of magnesium oxide, but greater and equivalent bioavailability of magnesium chloride, lactate and aspartate (8).

The relative absorbability and bioequivalence of magnesium amino acid chelate, magnesium citrate and magnesium oxide were compared with placebo in a randomised double-blind study in 51 healthy volunteers (9). The study concluded that the organic forms of magnesium (citrate and amino-acid chelate) are more absorbable than magnesium oxide or placebo, as assessed by the 24 hour urinary excretion after 60 days of daily supplementation (9). In this study, magnesium citrate was found to be the most bioavailable preparation as it resulted in the greatest serum magnesium concentrations following both acute and daily supplementation (9). Another small study in 17 healthy volunteers also concluded that magnesium citrate was more soluble and bioavailable than magnesium oxide (10).

In a small study in 3 groups of 8 healthy volunteers, two formulations of magnesium-L-aspartate were compared with magnesium oxide with respect to bioavailability and stool frequency. Magnesium oxide showed significantly lower absorption than magnesium-L-aspartate. However, plasma magnesium remained the same throughout the treatment periods (11). The difference in stool frequency between the groups was not statistically significant (11).

Table 1 Examples of Oral Magnesium Preparations Available in the UK. (NB other forms, brands or suppliers may be available). It should be noted that swapping between magnesium preparations on a mmol for mmol basis requires caution, as they have differing bioavailability and may not have an equivalent therapeutic effect. They need to be titrated to the maximum tolerated dose with monitoring of magnesium serum levels.

<table>
<thead>
<tr>
<th>Magnesium (Mg²⁺) salt and form</th>
<th>Supplier (Brand)</th>
<th>Licensed status in UK</th>
<th>Form and strength of salt (where available)</th>
<th>Mg²⁺ content in dosage form mg</th>
<th>Mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium-L-aspartate³,¹²,¹³</td>
<td>KoRa Healthcare Ltd (Magnaspartate®)</td>
<td>Prescription only medicine</td>
<td>6.5g oral powder</td>
<td>243</td>
<td>10</td>
</tr>
<tr>
<td>IDIS World Medicines (Magnesiocard®)</td>
<td>Unlicensed medicine</td>
<td>Granules</td>
<td>121.5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>IDIS World Medicines (Magnesiocard®)</td>
<td>Unlicensed medicine</td>
<td>615mg tablets</td>
<td>60.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Magnesium carbonate³,¹³,¹⁴</td>
<td>Martindale Pharma</td>
<td>Unlicensed medicine</td>
<td>100mg capsules</td>
<td>25.06</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500mg capsules</td>
<td>125.31</td>
<td>5.15</td>
</tr>
<tr>
<td>IDIS World Medicines</td>
<td>Unlicensed medicine</td>
<td>500mg capsules</td>
<td>144.58</td>
<td>5.93</td>
<td></td>
</tr>
<tr>
<td>Magnesium citrate³</td>
<td>IDIS World Medicines (Magnesium Diasporal 300®)</td>
<td>Unlicensed medicine</td>
<td>1830mg granules</td>
<td>295.7</td>
<td>12</td>
</tr>
</tbody>
</table>

Available through NICE Evidence Search at [www.evidence.nhs.uk](http://www.evidence.nhs.uk)
<table>
<thead>
<tr>
<th>Medicine</th>
<th>Manufacturer</th>
<th>Status</th>
<th>Concentration</th>
<th>Magnesium Content (mmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium chloride²</td>
<td>Martindale Pharma</td>
<td>Unlicensed medicine</td>
<td>100mg/ml solution</td>
<td>0.5 mmol/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200mg/ml solution</td>
<td>1 mmol/ml</td>
</tr>
<tr>
<td>Magnesium Hydroxide¹⁵,¹⁶,¹⁷,¹⁸</td>
<td>Omega Pharma Ltd (Phillips' Milk of Magnesia®)</td>
<td>Not licensed for hypomagnesaemia. Licensed as an antacid and a laxative.</td>
<td>83mg/ml liquid solution</td>
<td>1.424 mmol/ml</td>
</tr>
<tr>
<td></td>
<td>Thornton and Ross Ltd</td>
<td>Not licensed for hypomagnesaemia. Licensed as an antacid and a laxative.</td>
<td>265mg/ml mixture solution</td>
<td>1.4 mmol/ml</td>
</tr>
<tr>
<td>Magnesium glycerophosphate¹³,¹⁴,¹⁹,²⁰,²¹,²²,²³,²⁴,²⁵</td>
<td>Special Products Limited (Maglyphos®) OR Altovida (Glysmag®) OR IDIS World Medicines</td>
<td>Unlicensed medicine</td>
<td>1g tablets or capsules*</td>
<td>97 4</td>
</tr>
<tr>
<td></td>
<td>Special Products Limited OR Altovida (Glysmag®) OR IDIS World Medicines</td>
<td>Unlicensed medicine</td>
<td>Liquid - varying quantity of salt to give the required quantity of Mg²⁺</td>
<td>24.3 mg/ml 1 mmol/ml</td>
</tr>
<tr>
<td></td>
<td>Martindale Pharma</td>
<td>Unlicensed medicine</td>
<td>Various concentrations of liquid available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arjun Products Ltd (Magnaphate®)</td>
<td>Borderline substance</td>
<td>1g tablets*</td>
<td>97.2 4</td>
</tr>
<tr>
<td></td>
<td>IDIS World Medicines</td>
<td>Unlicensed medicine</td>
<td>97.2mg capsules*</td>
<td>9.4 0.4</td>
</tr>
<tr>
<td>Magnesium L-lactate dehydrate²⁶,²⁷</td>
<td>Durbin (Mag-Tab SR®)</td>
<td>Unlicensed medicine</td>
<td>Sustained release tablet</td>
<td>84 3.5</td>
</tr>
<tr>
<td>Magnesium oxide¹³,¹⁴</td>
<td>Martindale Pharma</td>
<td>Unlicensed medicine</td>
<td>Made to order in strength required (e.g. Magnesium oxide 100mg capsules containing approximately 60mg magnesium (2.5mmol))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IDIS World Medicines</td>
<td>Unlicensed medicine</td>
<td>140mg capsules</td>
<td>84 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>160mg capsules</td>
<td>96 4</td>
</tr>
<tr>
<td>Magnesium sulphate¹⁴</td>
<td>Martindale Pharma</td>
<td>Unlicensed medicine</td>
<td>98.6mg/ml solution</td>
<td>0.4 mmol/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400mg/ml mixture</td>
<td>2.2 mmol/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250mg/ml</td>
<td>1.6 mmol/ml</td>
</tr>
</tbody>
</table>
Small Studies and Case Reports
A small retrospective study published only in abstract form, compared the efficacy of magnesium-L-aspartate with intravenous magnesium and oral magnesium glycerophosphate for the treatment of hypomagnesaemia in four patients with short bowel syndrome (SBS). These four patients were receiving intravenous magnesium 20mmol fortnightly and magnesium glycerophosphate 12 mmol daily to maintain their plasma magnesium levels above 0.5mmol/L. These treatments were stopped and magnesium-L-aspartate (10mmol per sachet) was commenced at a dose of one sachet daily, and the dose was gradually increased to between three and five sachets daily. The mean plasma magnesium levels were not significantly different between the two groups and the authors conclude that magnesium-L-aspartate may be an effective way of treating hypomagnesaemia in SBS patients. In addition, magnesium-L-aspartate was well tolerated with no reports of increased stoma output (28). However, this was a very small study with a comparative open design. In addition the doses received by each patient are not clearly stated, and could range from 10 to 50mmol per day.

A small study, awaiting full publication, evaluated patient-reported outcomes and biochemical data following the introduction of magnesium lactate in the treatment of Gitelman Syndrome (GS). A questionnaire was used to evaluate the experiences of 28 patients whose usual formulation was replaced with slow release magnesium lactate. Preliminary results, available as a poster presentation, suggest an improvement in the symptoms of GS, improved mean serum magnesium and potassium levels, and improved side effects compared with the previous magnesium preparation. The authors concluded that slow release magnesium is particularly appropriate for those with GS where large doses of magnesium may be required to maintain adequate serum magnesium levels. (29). It has been suggested that sustained-release preparations of magnesium are preferable to standard preparations of magnesium for treating hypomagnesaemia, as they allow the use of lower doses and are thereby less likely to cause diarrhoea (30,31).

One published case report was identified where a 39 year old patient with hypomagnesaemia due to malabsorption was given increasing doses of magnesium glycerophosphate, to a maximum of 108mmol of magnesium per day (32). This failed to maintain adequate serum magnesium concentrations and the patient required several intravenous magnesium “top ups” because of repeated episodes of symptomatic hypomagnesaemia (32). The patient was changed to magnesium oxide, equivalent to 67.5mmol of magnesium per day, which maintained her magnesium between 0.58mmol and 0.62mmol/litre and she was asymptomatic (32). The authors comment that they do not know the reason for this improved absorption in this patient, but suggest magnesium oxide may be better absorbed than magnesium glycerophosphate in patients with a shortened small bowel (32). However, in another case report a 65 year old patient with short bowel syndrome and hypomagnesaemia was given an initial trial of magnesium glycerophosphate (33). This was insufficient to maintain her serum magnesium levels and she required frequent “top ups” with intravenous magnesium (32). She was therefore switched to magnesium oxide supplementation but despite this the frequency of intravenous magnesium “top ups” was not reduced (33).

In a case report of hypomagnesaemia associated with omeprazole, intravenous magnesium normalised the plasma magnesium levels, and the patient was switched to oral magnesium glycerophosphate. At a follow up appointment the plasma magnesium levels where found to be low despite magnesium glycerophosphate treatment (34). They reverted to normal after omeprazole was stopped, even after magnesium glycerophosphate was stopped. In a further case report of hypomagnesaemia due to omeprazole, magnesium glycerophosphate was given, but the patient developed hypomagnesaemia whenever supplements were stopped. Drug review raised the possibility that omeprazole may be causing hypomagnesaemia. After the omeprazole was stopped the patient's magnesium level remained normal without supplementation (34).

Adverse effects
Adverse effects of oral magnesium salts include gastrointestinal irritation and watery diarrhoea (a major dose limiting adverse effect) (1). Chronic diarrhoea from long term use may result in electrolyte imbalance (1). The use of sustained-release preparations (e.g. Mag-Tab SR® containing Magnesium L-lactate dihydrate) may allow the use of lower doses, which minimises diarrhoea (31). This may be important in the treatment of difficult to treat causes of hypomagnesaemia such as renal hypomagnesaemia (35). Parenteral therapy may be preferred in patients with poor gastrointestinal

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absorption of magnesium or who are unable to tolerate oral supplements (usually because of diarrhoea) (1).

Summary

- Magnesium-L-aspartate (Magnaspartate®) is the preferred choice for the treatment and prevention of magnesium deficiency when clinically appropriate as it is the only UK licensed oral magnesium preparation.
- If magnesium-L-aspartate (Magnaspartate®) is not effective in raising magnesium levels or if it is poorly tolerated it is reasonable to try an alternative oral magnesium preparation, if the patient's condition allows.
- Robust evidence of the superiority of one oral magnesium preparation over another does not exist; therefore it is not possible to recommend one particular preparation over another on the basis of efficacy and safety.
- Large scale clinical outcome studies are needed to compare the different oral magnesium preparations in patients with hypomagnesaemia.
- Information from the small studies available suggests there are differences in the bioavailability of some magnesium salts.
- Factors affecting the choice of a second line preparation may include local availability, patient tolerability, and price. Examples of oral magnesium preparations which are available in the UK are given in Table 1.
- Caution should be exercised when switching between magnesium preparations. Swapping on a mmol for mmol basis may not result in an equivalent therapeutic effect as magnesium preparations have differing bioavailability. The new preparation needs to be titrated to the maximum tolerated dose with monitoring of magnesium serum levels. Tolerability of a particular preparation may limit the dosage.
- The use of sustained-release preparations (e.g. Mag-Tab SR® containing Magnesium L-lactate dihydrate) may allow the use of lower doses, which minimises the risk of diarrhoea.

Limitations

This Q&A is not intended as a guideline for the treatment of hypomagnesaemia. A detailed discussion of the causes of hypomagnesaemia is beyond the scope of this Q&A. The list of oral magnesium preparations listed in table 1 is not exhaustive and other preparations may be available.

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35. Professor of Nephrology, Cambridge Institute for Medical Research. Personal communication. 12/5/2015

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**Search strategy**

- **Medline [Limit to: Publication Year 2013-2015]**
  - exp MAGNESIUM AND exp MAGNESIUM COMPOUNDS AND exp MAGNESIUM DEFICIENCY
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  - ("magnesium compounds"[MeSH Terms] OR ("magnesium"[All Fields] AND "compounds"[All Fields]) OR "magnesium compounds"[All Fields]) AND ("magnesium deficiency"[MeSH Terms] OR ("magnesium"[All Fields] AND "deficiency"[All Fields]) OR "magnesium deficiency"[All Fields])
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- **Cochrane Library "magnesium", "hypomagnesaemia"**
- **In-house databases and resources**
- **Manufacturers/suppliers:**
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  - Clinical Knowledge Summaries “magnesium”, “hypomagnesaemia”
  - NHS Evidence “magnesium”, “hypomagnesaemia”, “magnesium glycerophosphate”, “magnesium oxide”
  - Google Scholar “oral magnesium preparations and hypomagnesaemia” and “comparison of oral magnesium preparations”
- Professor of Nephrology, University of Cambridge.