University Hospitals of North Midlands NHS Trust | North Staffordshire Combined Healthcare NHS Trust | Staffordshire and Stoke on Trent Partnership NHS Trust | NHS North Staffordshire Clinical Commissioning Group | NHS Stoke-on-Trent Clinical Commissioning Group

New Medicines Committee Briefing

January 2018

Magnaspartate 243mg Powder for Oral Solution

Magnesium aspartate (Magnaspartate®) is to be reviewed for use within:

Primary Care	**√**
Secondary Care	√

Summary:

- Magnaspartate® is licenced for treatment and prevention of magnesium deficiency, as diagnosed by a doctor.[1]
- Magnaspartate® is indicated in adults, children and adolescents aged from 2 years.[1]
- Magnaspartate® is cheaper than magnesium glycerophosphate (Magnaphate and Neomag®
- There are no comparative studies to show superiority of one magnesium salt over another.[2]
- Magnesium glycerophosphate is currently the oral magnesium salt recommended on the North Staffordshire Joint Formulary and recommended for maintenance or mild magnesium deficiency in The Bedside Clinical Guidelines Partnership Medical Guidelines 2016 – 17 for hypomagnesaemia[3]
- Neomag® is the brand of magnesium glycerophosphate currently stocked at UHNM pharmacy and has recently been granted a product licence.[4]
- Magnaphate® (unlicensed) is the magnesium glycerophosphate currently recommended for Primary Care use on the Joint Formulary but is classed as a food supplement.

Formulary application

Dr Sathiavageeswaran has requested Magnesium Aspartate to be considered for inclusion in the North Staffordshire Joint Formulary for the correction of hypomagnesaemia. He intends that it be initiated in the hospital setting and subsequently continued in primary care.

Dr Mahesh noted that there are no published clinical trials comparing magnesium aspartate with placebo or active comparator or magnesium glycerophosphate for preventing recurrent hypomagnesaemia after treatment with intravenous magnesium. He stated that Magnaspartate is the preferred choice for both adults and children as it is the only licensed preparation available. (Neomag is also licensed). In his application he stated that magnesium glycerophosphate costs £84.50 for 120mmol (30 tablets x 4mmol) compared to £ 8.95 for 100 mmols (£10.74 for 120 mmols) of magnesium aspartate.

Dr Sathiavageeswaran estimates 30 new patients per month to be given an acute course.

Consultants submitting application: Dr Maheshi Sathiavageeswaran
(Consultant in Diabetes and Endocrinology)
Clinical Director supporting application: Dr George Varughese
(Consultant in Diabetes and Endocrinology)

Background [3, 5]

Hypomagnesaemia is an electrolyte disturbance in which there is a low level of magnesium in the blood.

Our current UHNM Bedside Clinical Guidelines Partnership Medical Guidelines[3] advise magnesium glycerophosphate orally, for maintenance or mild magnesium deficiency.
The Bedside Clinical Guidelines Partnership Medical Guidelines 2016 – 17 state:
Severe Defecit: Serum Mg2+ <0.5 mmol/L, **Moderate Defecit**: Serum Mg2+ 0.5–0.7 mmol/L
Mild Defecit: Magnesium is largely intracellular so mild deficiency can occur with a normal serum concentration, but urine excretion will be reduced: urine Mg2+/urine creatinine <0.1 = deficiency; <0.05 = severe deficiency, except if secondary to renal loss.

Magnaspartate® gained its marketing authorisation in Nov 2014 while Neomag® got license in Jan 2017. There are a number of magnesium supplements available such as Magnaphate® (classed as a food substance so unlicenced for hypomagnesaemia).

Magnaspartate® was granted a marketing authorisation under a bibliographic application; as such no new clinical or non-clinical efficacy studies were required by the Medicines and Healthcare products Regulatory Agency (MHRA) to support the application.

The applicant company (KORA Pharmaceuticals) additionally conducted a comparative aqueous solubility test comparing Magnaspartate® to magnesium glycerophosphate and magnesium oxide which demonstrated Magnaspartate® had the greater solubility [5] This is one of the reasons why the formulary application has been put forward.

Magnaspartate ® is cheaper than Neomag®

Current formulary status

Magnesium Aspartate is not on the current North Staffordshire Joint Formulary

9.5.1.3 Magnesium			
Magnesium glycerophoshate	**2**	**Magnaphate® recommended in Primary Care**	
Magnesium sulphate			

Therapeutic class and mode of action [1]

Mineral Supplement.
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

Licensed indications [1]

Magnaspartate® is indicated in adults, children and adolescents aged from 2 years for the treatment and prevention of magnesium deficiency, as diagnosed by a doctor.

Dosage and administration [1]

Adults (> 18 years): 1-2 sachets daily (243-486 mg magnesium or 10-20 mmol magnesium)
Children and adolescents: 10 to 18 years: 1 sachet daily, (243 mg magnesium or 10 mmol magnesium)
Children: 4-10 years: One level 5ml spoon daily (109 mg magnesium) or one sachet daily (243 mg magnesium).
Children: 2 to 4 years: One level 5ml spoon daily. (109 mg magnesium or 4.5mmol 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.
There is no dose adjustment necessary in patients with mild to moderate renal impairment.
Elderly: No dose adjustment is necessary.

Method of administration
Magnaspartate can be dissolved in 50-200mL water, tea or orange juice. For oral use

Safety and adverse effects [1]

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)

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.

Contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Frequent and long-term use of Magnaspartate 243 mg may be harmful to the teeth (caries).

Drug Interactions [1]

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

Presentation [1]

Powder for oral solution
White powder with a peach/apricot-like flavour.
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

Patent Status

None available

Guidance and Evidence Summary

NICE Guidance	Yes

Preventing recurrent hypomagnesaemia: oral magnesium glycerophosphate

Evidence summary [ESUOM4] Published date: January 2013[6]

No published clinical trials comparing the efficacy of oral magnesium glycerophosphate with placebo or any form of active treatment for preventing recurrent hypomagnesaemia after treatment with intravenous magnesium were identified. The only evidence found was from 3 case reports describing

the use of oral magnesium glycerophosphate for preventing recurrent hypomagnesaemia in adults after intravenous treatment.
Two of the 3 case reports concerned patients who had short bowel syndrome due to surgical resection. In both these patients, oral magnesium glycerophosphate was not sufficient to maintain serum magnesium levels after initial intravenous treatment. In 1 patient, switching from oral magnesium glycerophosphate to oral magnesium oxide resulted in maintenance of serum magnesium levels, but in the other patient this was still not sufficient and intravenous magnesium top ups were needed every 3–6 months. The third case report was of a patient with hypomagnesaemia associated with proton pump inhibitor use. In this patient, magnesium levels remained low after oral supplementation with magnesium glycerophosphate but reverted to normal after the proton pump inhibitor was discontinued, even after the magnesium supplement was stopped.
No studies of oral magnesium glycerophosphate for preventing recurrent hypomagnesaemia in children after intravenous treatment were identified.
The most frequently cited side effect of magnesium salts is diarrhoea.
The following information has become available since this ESUOM was produced.

July 2015: Availability of a licensed magnesium salt
A licensed magnesium product has now been launched in the UK. Magnaspartate is indicated for treating and preventing magnesium deficiency. The cost of Magnaspartate (excluding VAT) is £8.95 for 10 sachets.
In line with the guidance from the General Medical Council (GMC), unlicensed or off-label medicines should be used only where there is no suitably licensed medicine that will meet the patient's need.

Scottish Medicines Consortium (SMC)	

Magnesium aspartate dihydrate equivalent to 243mg (10mmol) of magnesium powder for oral solution (Magnaspartate®) SMC No. (1042/15) (Issued 05 June 2015)

Magnesium aspartate dihydrate (Magnaspartate®) is accepted for use within NHS Scotland for the treatment and prevention of magnesium deficiency, as diagnosed by a doctor.

This is the first licensed oral magnesium product to be available in the UK for the treatment and prevention of magnesium deficiency. Magnesium supplementation has previously been available as a food supplement.

Magnesium glycerophosphate 4mmol chewable tablet (Neomag®) SMC No 1267/17 (issued 4 August 2017)

Magnesium glycerophosphate (Neomag®) is accepted for use within NHS Scotland as an oral magnesium supplement for the treatment of patients with chronic magnesium loss or hypomagnesaemia as diagnosed by a doctor. Magnesium glycerophosphate is also indicated for adult patients with hypomagnesaemia due to the concomitant administration of loop and thiazide diuretics or other drugs which cause hypomagnesaemia.

Unlicensed tablet formulations of magnesium glycerophosphate have been used in the NHS in Scotland. This product provides a licensed preparation at a similar cost. Published 11 September 2017

All Wales Medicines Strategy Group (AWMSG)	

Magnesium aspartate dihydrate (Magnaspartate®) is recommended as an option for use within NHS Wales for the treatment and prevention of magnesium deficiency, as diagnosed by a doctor, in adults, children and adolescents aged from two years.

Regional Drug and Therapeutic Centre (RDTC)	**no**

Midlands Therapeutics Review and Advisory Committee (MTRAC)	**no**
Cost Analysis	

Brand	Pack size	UHNS (incl. VAT)	Primary Care (ecl. VAT
MAGNASPARTATE	10 sachets		£9.95
NEOMAG	50 tablets		£22.77
MAGNAPHATE	50 tablets		£19.87
MagnaPhos	200ml		£37.87

Drug	Brand/strength	Dose	Cost (Exc VAT)	Cost comparison Mg/dose (ex VAT)
Magnesium Aspartate	Magnaspartate 1 sachet = 10 mmol of magnesium	**Adults (> 18 years):** 1-2 sachets daily (243-486 mg magnesium or 10-20 mmol magnesium)	£8.95/10 sachets	89.5 pence/dose (10mmol) **= £1.78 for** 20mmol (1 day course)
Magnesium Glycerophosphate	Neomag Each chewable tablet contains 4mmol of magnesium.	**Adults (> 18 years):** Starting doses for adult patients are recommended as 4-8 mmol (1-2 tablets) x 3 times a day. This equates to a total dose of 12 to 24 mmol per day taken in divided doses.	£22.77/50 tablets	45.5 pence/tablet (4mmol) **= £2.73 for** 24mmol (1 day course)
Magnesium Glycerophosphate	Magnaphate Each chewable tablet contains 4mmol of magnesium	Marketed as a borderline substance unlicensed 2 tabs TDS (8mmol TDS)	£19.87/50 tablets	40 pence/tablet (4mmol) **= £2.38 for** 24mmol (1 day course

Expenditure:

UHNM Usage and Expenditure for Oct16-Sep17

Brand	UHNM Royal Stoke TOTAL EXPENDITURE (VAT applied as appropriate)	UHNM County Hospital TOTAL EXPENDITURE (VAT applied as appropriate)	UHNM TOTAL EXPENDITURE (VAT applied as appropriate)
MAGNASPARTATE	**£1,791.53**	**£2,364.60**	**£4,156.13**
NEOMAG	**£28,105.43**	**£11,659.36**	**£39,764.79**
MAGLYPHOS (UNLICENSED)	**£715.62**	**£0.00**	**£715.62**
	£30,612.58	**£14,023.96**	**£44,636.54**

North Staffordshire CCG Magnesium Aspartate/Gycerophosphate dispensed Oct 2016 – Sept 2017

		Values	
Magnesium Type	**BNF Name**	**Sum of Total Nic**	**Sum of Number of sachets, tablets**
Magnesium Aspartate	Mag Aspartate (Mag 10mmol)_Oral Pdr Sach	£854.74	955
	Magnaspartate(Mag 10mmol)_Pdr Sach 243mg	£667.67	746
Magnesium Aspartate Total		**£1,522.41**	**1,701**
Magnesium Glycerophosphate	Mag Glycerophos_Tab Chble 97.2mg (4mmol)	£3,969.20	9,923
	Mag Glycerophos_Tab Chble 97.2mg S/F	£4,709.54	8,218
	Mag Glycerophos_Tab Chble 97.2mgS/F(Old)	£12,741.82	9,166
	MagnaPhate_Tab Chble 97.2mg	£16,192.14	35,760
Magnesium Glycerophosphate Total		**£37,612.70**	**63,067**
Grand Total		**£39,135.11**	**64,768**

References

[1] Summary of Product Characteristics – Magnaspartate®. Magnesium Aspartate 243mg (10mmol Magnesium) powder for oral solution. Accessed via http://www.medicines.org.uk/emc/medicine/30238 on 07.12.2017 [date of revision of the text: 07/2016]

[2] How is acute hypomagnesaemia treated in adults?; UKMI Medicines Q & A 17/07/2017 https://www.sps.nhs.uk/articles/how-is-acute-hypomagnesaemia-treated-in-adults/ Accessed:12/12/2017

[3] University Hospitals of North Midlands NHS Trust Bedside Clinical Guidelines Partnership Medical Guidelines 2016 – 17 Accessed via: http://uhns/media/881877/170907%20Medical%20guidelines%202016-17%20UHNMv1.2.pdf

[4] Summary of Product Characteristics - Neomag®.Magnesium Glycerophosphate chewable tablets 4mmol (97mg Magnesium) Accessed via https://www.medicines.org.uk/emc/product/2678 on 07.12.2017 [date of revision of the text: 10/01/2017]

[5] What oral magnesium preparations are available in the UK and which preparation is preferred for the treatment and prevention of hypomagnesaemia ?; UKMI Medicines Q&A 08/04/2015 https://www.gwh.nhs.uk/media/226663/oral-magnesium-preparations-for-the-treatment-and-prevention-of-hypomagnesaemia-ukmi-qas.pdf

[6] Preventing recurrent hypomagnesaemia: oral magnesium glycerophosphate. Evidence summary [ESUOM4] Published date: January 2013. Access via: https://www.nice.org.uk/advice/esuom4/chapter/Overview-for-healthcare-professionals