HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

7 January 2009

Review of product listed for a limited duration in accordance with the decree of October 27, 1999 (Official Journal of October 30, 1999) and the order of December 1, 2006 (OJ of December 21, 2006)

SPASMAG vials for oral solution
Pack of 30 vials of 5 ml (CIP: 329 263-5)

SPASMAG tablets for oral solution
Pack of 30 tablets (CIP: 329 397-1)
Pack of 42 tablets (CIP: 329 398-8)

SPASMAG capsules
Pack of 60 capsules (CIP: 323 690-9)

Applicant: GRIMBERG

Magnesium sulphate
Saccharomyces cerevisiae yeast

Date of Marketing Authorisations:
SPASMAG vials for oral solution: MA validated Sept 21, 1976, initial approval November 26, 1955
SPASMAG tablets for oral solution: April 7, 1987
SPASMAG capsules: May 6, 1980

Reason for request: renewed inclusion on the list of medicines reimbursed by National Insurance.

The provisional opinion issued by the Transparency Committee on June 11, 2008 has been amended subsequent to a review of the actual clinical benefit of products containing magnesium combined with another active ingredient.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

Magnesium sulphate
Saccharomyces cerevisiae yeast

1.2. Indications

“Known magnesium deficiency, isolated or associated.”

1.3. Dosage

Adults: 3 vials daily or 5 to 7 capsules daily or 3 tablets daily
Children: 9.6 to 28.8 mg/kg/day, i.e. 1 to 3 vials daily or 1 to 7 capsules daily or 1 to 3 tablets daily

The normal duration of treatment is 1 month.

2 REMINDER OF THE COMMITTEE'S OPINION AND LISTING CONDITIONS

Opinion of November 19, 1999

The actual clinical benefit in comparison to other products and treatments available is not sufficient to warrant reimbursement.

Opinion of May 11, 2005

The actual clinical benefit of these products in their indication is moderate.

Opinion of June 11, 2008

The actual clinical benefit of SPASMAG products is:

- moderate, solely in cases of known deficiency induced by a severe enteropathy, tubulopathy or nephrotic syndrome.
- insufficient in all other cases.

Provisional opinion pending the reevaluation of magnesium-based products combined with another active ingredient.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2008)

A	Alimentary tract and Metabolism
A12	Mineral supplements
A12C	Other mineral supplements
A12CC	Magnesium
A12CC02	Magnesium sulphate

3.2. Medicines in the same therapeutic category

EFIMAG sachets (magnesium pidolate)
MAG 2 (magnesium pidolate)
MEGAMAG 45 mg capsules (magnesium aspartate)

4 UPDATING WITH DATA OBTAINED SINCE PREVIOUS OPINION

In the context of a reevaluation of products containing a combination of magnesium with another active ingredient, the company was called upon to justify the benefit of a combination of a magnesium salt with saccharomyces cerevisiae yeast.

Given that saccharomyces cerevisiae is an inactivated yeast used in a number of food preparations, the committee considers saccharomyces cerevisiae as an excipient.

5 DRUG USAGE DATA

According to IMS data (CMA August 2008), 262,000 prescriptions of SPASMAG have been delivered. The most common reasons for prescription were malaise and fatigue (18%), nerve and osteomuscular symptoms (9%), depressive episodes (6%), and abnormal involuntary movements (4%). The average daily dosage is 4 units. These prescriptions are therefore mostly outside the scope of the MA.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

A known magnesium deficiency can be the cause of:
- mental disorders: apathy, delirium, personality disorders, depression.
- cardiovascular disorders: ventricular and supraventricular arrhythmia, torsade de pointes.
- neuromuscular symptoms: spasmophilia, cramps.
- neurological disorders: vertigo, dysphasia, abnormal movement, convulsions, hemiparesia.
- electrolyte disorders: hypokalaemia, hypocalcaemia.

In some cases it can progress towards a deterioration in the quality of life or a disability.
However, it can be difficult to distinguish between a known magnesium deficiency and other conditions when diagnosing.

These products are intended for symptomatic treatment.

The use of magnesium is justified in known magnesium deficiencies.
At the usual dosages, these products do not appear to expose patients to serious and/or frequent adverse effects.
The efficacy/adverse effects ratio of these products in the treatment of known magnesium deficiency is moderate.

Known magnesium deficiency, i.e. confirmed by labwork, corresponds essentially to chronic situations, the cause of which may be digestive (severe enteropathy) or nephrological (tubulopathy or nephrotic syndrome). These situations must be managed with a magnesium salt in the long term.

The actual benefit of SPASMAG products is:
- moderate, solely in cases of known magnesium deficiency induced by a severe enteropathy, tubulopathy or nephrotic syndrome,
- insufficient in all other cases.

6.1. Therapeutic use

There is no consensus on the means of evaluating magnesium status.

Magnesemia does not reflect the state of deficiency well as magnesium is an intraerythrocytic cation and only a small proportion of the body's magnesium is found in the plasma.
However, in practice, a magnesium deficiency is generally evaluated by magnesemia and if there are any doubts as to whether the cause is renal or extrarenal, by the level of magnesium in the urine over 24 hours. In a clinical context suggesting a deficiency, other tests such as intraerythrocytic magnesium levels can be conducted to confirm depletion, despite subnormal magnesemia.

Hypomagnesemia is also closely related to metabolic disturbances of other electrolytes, particularly calcium and potassium[1].

Apart from known magnesium deficiencies due to digestive or renal problems, it is not appropriate to prescribe magnesium.
Moderate magnesium deficiencies can be corrected by a diet rich in green vegetables, meat, cocoa, milk and pulses.

6.2. Target population

Known chronic hypomagnesaemia requiring long-term oral treatment is very rare. According to the French Society of Enteral and Parenteral Nutrition (SFNEP):

- digestive causes (severe enteropathy) concern around 2,000 patients,
- nephrological causes of renal magnesium leakage correspond to certain tubulopathies and certain nephrotic syndromes. They concern around 1,000 patients.

To conclude, according to experts, the target population actually benefiting from magnesium is not thought to exceed 3,000 patients.

6.3. Transparency Committee recommendations

The Transparency Committee recommends inclusion of SPASMAG on the list of medicines reimbursed by National Insurance, only in cases of known magnesium deficiency induced by severe enteropathy or associated with a tubulopathy or nephrotic syndrome, at MA-recommended doses.

Packaging: appropriate for the MA's prescription requirements.

Reimbursement rate: 35%

[1] SHILS M.E, in modern Nutrition in health and disease 1998; ninth edition: 169-192