

## 1.1. Omeprazole, esomeprazole and hypomagnesaemia

### Introduction

Omeprazole (Losec<sup>®</sup>) is a proton pump inhibitor (PPI) which has been registered in the Netherlands since November 1988. It is indicated for use in gastroduodenal ulcer disease, acid relate dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome. Furthermore omeprazole is used as prophylactic treatment in people at risk for drug related erosive or ulcer gastric disorders. With 1,025,000 users in 2007 omeprazole is by far the most used PPI [1]. Among its most common adverse reaction are headache and gastro-intestinal symptoms [2]. Besides omeprazole, also its purified S-isomere esomeprazole is marketed (Nexium<sup>®</sup>). Magnesium is involved as cofactor in many enzyme regulated reactions and body magnesium levels are a balance between intestinal absorption and renal excretion [3]. Intestinal absorption takes place through passive paracellular diffusion as a constant fraction of ingested magnesium and through active receptor mediated transcellular uptake [4]. Magnesium has important effects on calcium homeostasis through decreased parathyroidal hormone secretion and diminished responsiveness of skeletal and renal tissue to parathyroidal hormone (PTH). Hypocalcaemia can in its turn lead to life-threatening cardiac arrhythmia or convulsions [3]. Hypomagnesaemia is not mentioned in the SmPCs for omeprazole [2]. This report describes the association between omeprazole and esomeprazole use and hypomagnesaemia.

### Reports

On February 7 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of hypomagnesaemia associated with the use of omeprazole (Table 1).

Table 1. Reports of hypomagnesaemia associated with the use of omeprazole.

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Remarks
A 74705 M, 58	omeprazole 20 mg od dyspepsia	salbutamole, hydrochloro- thiazide, beclomethasone, metoprolol	Hypomag- nesaemia (0.35) hypocalcaemia	days withdrawn, recovered	recurrence of hypomag- nesaemia after use of esomeprazole unspecified chemotherapy for unspecified disorder in medical history.
B 80042 M, 61	omeprazole 10mg	atorvastatin bisoprolol lisinopril	hypomagnesa emia cardiac arrhythmia convulsions	10 years withdrawn recovered	serious, hospi- tation, life-threat- ening aspects Intestinal carcinoma in medical history

Patient A was referred to a nephrologist because of low calcium (1.65) for which a renal cause was excluded. Suspicion on a reduced intestinal absorption of magnesium was confirmed by a raised magnesium in 24-hour stool. Withdrawal of omeprazole led to recovery for low magnesium and low calcium, which reportedly had been reduced for over a year. Serum magnesium however decreased again from 0.90 to 0.57 after start of esomeprazole. Discontinuation of this drug led to normalisation of serum magnesium levels.

Patient B presented with a life threatening unspecified cardiac arrhythmia which necessitated repeated electric cardioversion and convulsions, according to the reporting pharmacist due to severely low serum magnesium. After referral to a university hospital where omeprazole was withdrawn, serum magnesium levels reportedly returned to normal values without specification of drug levels.

An effect of the malignancy in both patients' medical history cannot be excluded. Unfortunately details such as the exact diagnosis, treatment and date of the reported neoplasm lack in the report. However given the lack of any antineoplastic therapy in the reported co medication suggests it to be an event in the past, unrelated to the hypomagnesaemia reported. Patient B's medical history includes an intestinal neoplasm (2004) which implies resection of a relatively large part of intestinal tissue, which may have been contributive to the impaired absorption of magnesium.

No cases of hypomagnesaemia related to use of other PPIs were reported to the Netherlands Pharmacovigilance Centre Lareb.

### **Other sources of information**

#### *Databases*

The database of the World Health organization (WHO) contained thirteen reports of hypomagnesaemia related to omeprazole use. In all but one cases omeprazole was rated as sole suspect drug. The number of cases does not result in disproportionality. Hypomagnesaemia associated with esomeprazole use was reported two times.

On February 2, 2009, the Eudravigilance database contained 65 reports of hypomagnesaemia related to omeprazole use, all rated to be serious. Thirty-three women were involved and 30 male patients. Age ranged from 15 to 84 years. Sex was not specified in two cases, age in six cases. In five cases life threatening aspects were the reason for a classification as a serious reaction, in 45 cases hospitalisation was indicated.

Esomeprazole was involved in fifteen cases reported to the Eudravigilance database. In five cases esomeprazole was the only PPI used. In six cases omeprazole use was reported. In four cases, probably concerning a reaction in one patient pantoprazole use was also reported.

#### *Literature*

Hypomagnesaemia, mostly after many year use of omeprazole has been the subject of a number of recent publications [4-6], describing in total five cases. The patients had symptoms of severe hypocalcaemia and hypomagnesaemia (seizures, cardiac arrhythmia, tetany, intensive vomiting leading to other electrolyte disturbances and psychiatric symptoms). Despite low serum calcium, parathyroid hormone in serum was decreased or normal, instead of an expected increase to raise serum calcium. Infusion of calcium and magnesium led to temporarily recovery, however after discharge calcium and magnesium serum levels decreased while PPI-treatment was maintained. Calcium and magnesium levels only normalised after withdrawal of PPIs. In one patient renewed hypomagnesaemia and hypocalcaemia occurred after start of esomeprazole[5]. In the cases presented by Epstein and Cundy both gastrointestinal disease leading to generalised disturbed absorption and renal loss of calcium were excluded [4,5].

After high dose oral administration during omeprazole use magnesium levels increased temporarily, probably through diffusion. Hence Cundy postulates the passive magnesium uptake to be intact, while active magnesium uptake through the active transport mechanism (TRPM6) is believed to be impaired due to omeprazole use. It is unclear whether the decreased function of TRPM6 is caused by factors which affect the entire population using PPIs, e.g. through lowering intestinal pH or that particular uses are susceptible by specific mutations in TRPM6 [4]. Magnesium lowering effects of other PPIs are not described in literature.

## Discussion

The relation between omeprazole use and hypomagnesaemia is supported by reported cases and three recent journal publications.

The two cases reported to the Netherlands Pharmacovigilance Centre Lareb are both well documented. In case A withdrawal of omeprazole led to recovery of a yearlong existing hypomagnesaemia.

The findings of clinical testing and the raised stool magnesium are in line with the impaired intestinal magnesium uptake suggested by Cundy. Furthermore the renewed hypomagnesaemia following start of omeprazole's s-isomere esomeprazole can be regarded as positive rechallenge. The publications on this subject describe hypomagnesaemia in only a limited number of patients, but due to clinical characteristics and extensive diagnostical elaboration a relation with PPI use is almost conclusive.

Cundy suggests the presence of a PPI class effect. Such a class effect cannot be excluded but cannot be concluded from the published data. However suspicion for the occurrence of hypomagnesaemia in PPI users is warranted. The association described is of high clinical relevance. The effects of hypocalcaemia induced by hypomagnesaemia are ultimately life threatening. Because of the slow depletion of magnesium stores, a relation with omeprazole use may remain unnoticed during clinical practice. Given the widespread use of omeprazole and a relatively large part of the population with pre-existing low magnesium stores due to poor nutritional intake [3], there is a large potential of severe morbidity in the population for omeprazole induced hypomagnesaemia. Special care for the population particularly at risk, such as patients with a poor nutritional state or conditions leading to impaired intestinal absorption, is warranted. Alternative gastric acid lowering therapies, such as H2 antagonists or intermittent PPI use, are available and usually well tolerated.

## Conclusion

The potential for hypomagnesaemia, disturbance of calcium homeostasis and its potentially life-threatening complications in populations at risk should be clearly expressed in the SmPC for all omeprazole and esomeprazole containing products.

## References

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6. Shabajee N, Lamb EJ, Sturgess I, Sumathipala RW. Omeprazole and refractory hypomagnesaemia. BMJ 2008;337:a425.

*This signal has been raised on April 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbg-meb.nl/cbg/en/default.htm](http://www.cbg-meb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*