IRISH MEDICINES BOARD

# Drug Safety NEWSLETTER

46TH EDITION

## Proton-pump inhibitors – Association with hypomagnesaemia with long term use

Proton-pump inhibitors* (PPIs) are indicated in the treatment of gastric and duodenal ulcers, NSAID-associated ulcers, gastro-oesophageal reflux, Zollinger-Ellison syndrome and in combination with anti-bacterial therapy for eradication of Helicobacter pylori. Some products are only indicated for short term use to treat reflux symptoms in adults (see individual Summaries of Product Characteristics [SPCs] on **www.imb.ie** for full details of licensed indications).

The Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency recently reviewed spontaneous adverse reaction reports and published case reports of hypomagnesaemia with PPIs, which indicated a causal relationship between hypomagnesaemia and long-term use of PPIs. Although the reported frequency of this effect is low, due to the extensive use of PPIs, the seriousness of some of the cases and the potential serious consequences of a delayed diagnosis, the product information for those products indicated for long term use will be updated to inform healthcare professionals and patients of this rare, but potentially serious risk.

Normal blood magnesium levels range from 1.8 to 3.0 mg/dL; clinical symptoms of hypomagnesaemia appear with levels below 1.5 mg/dL and include mainly neuromuscular symptoms such as asthenia, muscle hyperexcitability, disorientation, convulsions and dizziness. The most frequent cardiovascular manifestations are ventricular arrhythmia and metabolic disturbances such as hypokalaemia and hypocalcaemia which may lead to tetany.

In most cases, patients presented with several symptoms of hypomagnesaemia and had been hospitalised in the preceding years, which may reflect the difficulty of linking these reactions with PPI intake. Symptoms of neuromuscular, cardiac and metabolic effects of severe hypomagnesaemia may begin insidiously and could be overlooked.

The mechanism of PPI-induced hypomagnesaemia is unknown however, most patients only presented with symptoms after long-term use of the drug (at least three months and in most cases after one year). Available data at this time supports the view that hypomagnesaemia is a class effect of PPIs associated with long term use.

### Advice to Healthcare Professionals

- For patients expected to be on prolonged treatment, or who take PPIs with digoxin, or drugs which may cause hypomagnesaemia (e.g. diuretics), health-care professionals should consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during treatment.
- PPIs should be considered as a possible cause of hypomagnesemia, particularly in patients who are clinically symptomatic.
- In the majority of reported cases, hypomag-nesaemia improved after magnesium replacement and discontinuation of the PPI.

**Key Message**

**PPIs may cause severe hypomagnesaemia with long term use. In patients expected to be on prolonged treatment and particularly if using other hypomagnesaemia-inducing medicines, healthcare professionals should consider measuring magnesium levels before and periodically during treatment.**

* *PPIs currently authorised in Ireland include omeprazole, esomeprazole, rabeprazole, pantoprazole and lansoprazole, see* ***www.imb.ie*** *for authorised product names.*

*References are available on request from the Irish Medicines Board.*

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## Metoclopramide – New recommendations for treatment of children

Metoclopramide* is an antiemetic. Its mechanism of action is unclear but it is thought to have both central action by blocking dopamine receptors and local effect on gastric muscle, stimulating contractility. It is authorised for use in adults for the treatment of disorders of the gastrointestinal tract associated with delayed gastric emptying such as reflux oesophagitis and hiatus hernia, nausea and vomiting associated with the administration of cytotoxic drugs and radiotherapy, for use in diagnostic procedures such as barium studies and duodenal intubations and to counteract gastric stasis associated with attacks of migraine.

The use in young adults (under 20 years) and children is currently restricted to the treatment of vomiting associated with radiotherapy and intolerance to cytotoxic drugs and as an aid to gastro-intestinal intubation. The risk of extrapyramidal disorders is outlined in the product information.

A recent European evaluation of the paediatric use of metoclopramide (in accordance with Article 45 of Regulation EC No. 1901/2006, as amended, on medicinal products for paediatric use) considered the efficacy and safety and in particular the risk of extraypyramidal disorders. Changes to the product information including the removal of the previously approved indications for children were recommended.

The new recommendations are as follows:

- Use of metoclopramide is now contraindicated in children less than 1 year of age, due to an increased risk of extrapyramidal disorders.
- Oral formulations of metoclopramide are not recommended in children and adolescents.
- Metoclopramide 5 mg/ml solution for injection is indicated for the treatment of postoperative nausea and vomiting for children from 1 year of age. For other indications, use in children and adolescents is not recommended.

A review of metoclopramide pharmacokinetic data and its safety profile in neonates (less than 1 month of age) and infants less than 1 year of age was carried out. Pharmacokinetic data showed that the clearance of metoclopramide tends to be reduced in neonates. The review of post marketing safety data showed that the risk of extrapyramidal disorders is increased in infants less than 1 year of age compared to children from 1 to 18 years of age. As a result of these data, use of metoclopramide is now contraindicated in children less than 1 year of age.

Due to limited efficacy and safety concerns, oral metoclopramide (tablets or suspension) is not recommended in children and adolescents.

For metoclopramide 5 mg/ml solution for injection, the indication postoperative nausea and vomiting has been added for children from 1 year of age as the benefit/risk in this indication is considered positive. The paediatric dose for metoclopramide 5 mg/ml solution for injection has been changed in accordance with this indication. The use of metoclopramide 5 mg/ml solution for other indications in children and adolescents is not recommended.

The process for implementation of these recommendations into the product information is ongoing with the marketing authorisation holders and should be completed in the coming months.

The safety of metoclopramide-containing medicines in children and adolescents 1 to 18 years will be further evaluated in a European procedure (Article 31 of Directive 2001/83/EC) that has recently been initiated. An update on the outcome of this evaluation will be provided when available, including information on any further recommendations and revisions to the product information.

Suspected adverse reactions associated with the use of metoclopramide should be reported to the IMB via the usual routes.

**Key Message**

**Metoclopramide is contraindicated in children under 1 year of age. Oral formulations are not recommended in children and adolescents. Intravenous metoclopramide is only indicated for the treatment of postoperative nausea and vomiting in children from 1 year of age.**

* *Products currently authorised in Ireland include Maxolon and Paramax*

## Gonadotrophin-releasing hormone agonists – Risk of depression

Gonadotrophin-releasing hormone (GnRH) agonists* are used for gonadal suppression in various sex-hormone-dependent conditions, including prostate cancer, breast cancer and endometriosis.

Following reports of severe depression and suicide from a Japanese survey of women with endometriosis treated with GnRH agonists[1], the marketing authorisation holder for leuprorelin performed an epidemiological study in the UK General Practice Research Database (GPRD). The study revealed an increased risk of incident depression in patients with endometriosis and prostate cancer treated with GnRH agonists. An increased risk of suicidal behaviour was also seen in patients with prostate cancer treated with GnRH agonists.

The PhVWP evaluated the available information relating to evidence of a possible increased risk of depression with these products, including data from the Japanese survey, the UK study and a previous assessment of the safety of leuprorelin based on a comprehensive review of relevant literature[1-11] and spontaneous adverse reaction reports. The GPRD study showed an incidence rate of incident depression in the range of 1 to 10 cases per 100 person-years in male and female patients with indications for GnRH agonist treatment.

In patients with endometriosis, use of GnRH agonists was associated with around a 50% increase in the risk of incident depression (relative risk (RR): 1.46; 95%CI: 1.12-1.89). The size of this risk overlaps with that seen in unexposed patients (RR 1.38; 95%CI: 1.29-1.48). In patients with prostate cancer, GnRH agonist use was associated with a RR of 1.97 (95%CI: 1.86-2.10) of incident depression. This RR is above that associated with prostate cancer itself (RR 1.45; 95%CI: 1.35-1.55). Similar results were obtained when comparing patients with past exposure to GnRH agonists. An increased risk of suicidal behaviour was observed in patients with prostate cancer treated with GnRH agonists, but results should be interpreted with caution due to the small number of events and potential biases related to the retrospective and observational nature of the study.

The review of literature[2-11] and spontaneous adverse reaction reports revealed that depression and mood changes are known risks related to the reduction in oestrogen/ testosterone levels during treatment with GnRH agonists.

The PhVWP assessment concluded that the available evidence suggests that GnRH agonists are associated with an increased risk of depression and mood change and that the product information should be updated to consistently reflect the available evidence.

### Advice to Healthcare Professionals

- There is an increased risk of incident depression, which may be severe, in patients undergoing treatment with GnRH agonists.
- Patients should be informed of this risk and advised to report any symptoms to their doctor. Patients should be treated as appropriate if symptoms occur.

**Key message**

**Some evidence suggests that GnRH agonists are associated with an increased risk of depression and mood changes. Patients should be advised accordingly.**

* *The GnRH agonists included in the review were buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin. Products authorised in Ireland include: Vantas, Synarel, Zoladex, Suprefact, Suprecur, Eligard, Prostap, Leuprorelin Rowex, Gonapeptyl, Decapeptyl.*

*References are available on request from the Irish Medicines Board*

### View the Drug Safety Newsletter online or via email

The IMB publishes an electronic version of the Drug Safety Newsletter on its website, **www.imb.ie**. Should you wish to receive an email alert notifying you that future editions of the newsletter are available online, please submit your request to **imbpharmacovigilance@imb.ie**. Alternatively the electronic version can be emailed directly to you. Signing up to this service will ensure you no longer receive a print version. The online edition is in PDF format, thus allowing you to save the newsletter and/or print specific pages. The online version will also contain hyperlinks to the product information and other documents on the IMB and EMA websites. By signing up to this environmentally friendly online service, you will receive prompt notification of publications and will assist the IMB to reduce postage, production and related costs.

## HMG-CoA reductase inhibitors – Risk of new onset diabetes in patients already at increased risk of developing diabetes

HMG-CoA reductase inhibitors*, commonly known as statins, are used to lower lipids in the blood. Following the publication of a meta-analysis which reported that therapy with statins overall was associated with a slightly increased risk for the development of new onset diabetes, the PhVWP conducted a review of this risk based on the available data.

The PhVWP concluded that statins may increase the risk of new onset diabetes in patients already at risk of developing the disease, but that overall the risk-benefit balance remains positive, given the benefit of statins in reducing major cardiovascular events.

In 2010, a clinical trial meta-analysis reported that statin therapy overall was associated with a slightly increased risk of new onset diabetes.[1] Although the risk identified was small (odds ratio 1.09 [95% CI 1.02–1.17]), given the extent of exposure, even a relatively small increase in the risk of new onset diabetes could potentially result in a significant number of additional cases of diabetes per year. Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.[1] However, the evidence suggests that risk depends markedly on individual risk factors. Comparison of studies across the statin class is limited by numerous factors including differences in patient populations, duration of study, and dose of statin used. Additionally, the endpoint used to diagnose diabetes varied in terms of frequency and time of analysis, and whether fasting blood glucose or, more rarely, HbA1c levels were measured. Importantly, a recent study[2] of the association between atorvastatin and new onset diabetes suggests that stratification of patients by risk factors may yield different conclusions to those drawn when considering the patient population as a whole.

While there is sufficient evidence to support an association between statin use and new onset diabetes, the risk appears to be mainly in patients already at increased risk of developing diabetes. Raised fasting blood glucose at baseline is a key factor in determining this increased risk and may be sufficient to identify those at risk. Other risk factors include a history of hypertension, raised triglycerides and raised body mass index at baseline.

There are limited data to support a further increased risk of diabetes with intensive high-dose atorvastatin or simvastatin therapy.[3] Given the important effect of patient characteristics on the risk of diabetes and the variability of the available studies, there are currently insufficient data to exclude any statin from the possibility of exacerbating the risk of new onset diabetes in a susceptible individual.

Despite the increased risk of new onset diabetes in susceptible individuals, studies clearly show a benefit of statins in reducing major cardiovascular events.[3, 4, 5] The overall benefits of statins strongly outweigh any risks, including in those at risk of diabetes and those with diabetes at baseline. However, steps should be taken to identify patients who are at risk, to detect the onset of new onset diabetes, and to manage the condition appropriately. Patients at risk should be monitored both clinically and biochemically. It was therefore agreed that a warning should be included in the product information of all statins authorised in the EU aiming to ensure monitoring of patients at risk.[6]

### Advice for healthcare professionals

- There is sufficient evidence to support an association between statin use and new onset diabetes.
- The risk appears to be mainly in patients already at increased risk of developing diabetes.
- Raised fasting blood glucose at baseline is a significant risk factor. Other risk factors include a history of hypertension, raised triglycerides and raised BMI at baseline.
- Patients at risk should be monitored both clinically and biochemically to ensure new onset diabetes is identified promptly if it occurs and managed appropriately.
- The reduced vascular risk from statin treatment outweighs the risk of diabetes, which is therefore not a reason for stopping statin treatment.

**Key message**

**Statins may increase the risk of new onset diabetes in patients already at risk of developing the disease. Patients at risk should be monitored. This risk is outweighed by the beneficial reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment.**

* *The active substances included in the review were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, see* ***www.imb.ie*** *for authorised products.*

*References are available on request from the Irish Medicines Board*

## Varenicline (Champix) and cardiovascular safety

Varenicline (Champix) is authorised for use throughout the EU for the treatment of smoking cessation in adults.

A study published in the Canadian Medical Association Journal in 2011 suggested that varenicline may be linked to potential for an increased risk of serious adverse cardiovascular events.[1] The study, a meta-analysis of randomised clinical trials involving 8,216 subjects, found a higher risk of serious adverse cardiovascular events in patients taking varenicline compared with placebo, although the events were rare in both groups (1.06% in the varenicline group versus 0.82% in placebo group). The events included heart attack, stroke, disruption of heart rhythm, heart failure and death related to cardiovascular problems. A difference in death rates was not seen between the two groups.

The Committee for Human Medicinal Products and its PhVWP did not consider it possible to draw robust conclusions from the meta-analysis due to methodological limitations, including the low number of events seen, the types of events counted, the higher drop-out rates in people receiving placebo, the lack of data on time to onset of events, and the exclusion of studies in which no-one had an event. The PhVWP concluded that that the slightly increased risk of cardiovascular events reported by the study's authors does not outweigh the benefits of varenicline and the results should be interpreted in a broader context, taking the beneficial long-term effects of smoking cessation into account.

The current product information already lists cardiovascular events as possible side effects of varenicline however additional information has been added to reflect the meta-analysis results and consolidate the information regarding cardiovascular risk. Patients taking varenicline should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction. The product information including the SPC is accessible on **www.ema.europa.eu**.

**Key Message**

**The benefit-risk balance of varenicline is unchanged and remains favourable. Additional information on the risk of cardiovascular events has been included in the product information.**

## Adverse Drug Reaction Reporting Experience during 2010

Following recent publication of the IMB's Annual Report for 2010, a summary overview of reporting experience is provided as feedback to healthcare professionals.

During 2010, the IMB received a total of 3,202 suspected adverse reaction reports occurring in Ireland from healthcare professionals, patient/consumers and pharmaceutical companies. This includes some 779 reports associated with the use of the pandemic A(H1NI) vaccines, as part of an enhanced surveillance system introduced in 2009 to monitor experience with their use at both national and EU level. The majority of these reports were received in the first quarter of 2010, coinciding with completion of the HSE H1N1 vaccination campaign in March 2010.

The IMB greatly appreciates the contribution of busy healthcare professionals in reporting suspected adverse reactions, facilitating the continued surveillance of the safety of medicines and in particular the prompt reporting of experience with use of Gardasil in the context of the HSE Human Papillomavirus (HPV) Schools Immunisation programme, initiated in May 2010. The reports provided were helpful in confirming that the national experience with use of Gardasil was consistent with the expected safety profile of the vaccine. While the time-consuming nature of form-filling and the provision of follow-up information to the IMB is recognised, the collection and evaluation of comprehensive reports is important to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines. Such reports are essential for the IMB to ensure that regulatory action/proposals take account of all available data.

The on-line reporting system, available to healthcare professionals and patients/consumers, continued to be a convenient method of reporting during 2010, with some 342 reports submitted by year end via this route. Access to the on-line reporting system is available through the IMB website at **www.imb.ie**.

Relevant, anonymised reports (i.e. serious, suspected cases) notified directly to the IMB by healthcare professionals were forwarded to the appropriate marketing authorisation holders (MAHs) and the European Medicines Agency for inclusion on the European database (Eudravigilance). The IMB also provided details of reports received to the WHO for inclusion on its international database.

## Adverse Reaction and Quality Defect Reporting including Herbal Medicines

The IMB monitors the safety and quality of all authorised medicines available on the Irish market on an on-going basis and part of this monitoring is carried out through review and evaluation of suspected adverse reactions and quality defects. The IMB website includes a facility for online reporting of quality defects and suspected adverse reactions associated with the use of medicinal products. Reporters can log on to www.imb.ie and follow the link to 'Online Reporting' on the website homepage where further instructions on how to complete the individual case report forms are available.

Alternatively, downloadable or hardcopy forms can be completed and returned to the IMB by 'freepost', further information is available on **www.imb.ie** or by phoning the IMB Pharmacovigilance Section on 01– 6764971 or emailing **imbpharmacovigilance@imb.ie**. With respect to quality defect reporting, the IMB Market Compliance Section may be contacted on 01 676 4971 or by emailing **recallsandqualitydefects@imb.ie**.

### Herbal Medicinal Products

Some plants contain substances that may be used to treat certain illnesses. Medicines that are made from these substances are known as herbal medicinal products or herbal medicines. In 2004 the European Commission introduced the Traditional Herbal Medicinal Products Directive to allow for the regulation of these 'traditional herbal medicines'. This Directive was subsequently written into Irish law and on April 30th 2011 this legislation came into force in Ireland. Under this legislation companies who wish to keep or place a traditional herbal medicinal product on the market in Ireland must seek to register this product with the IMB.

Even though herbal medicines are derived from plant substances and considered as 'natural' products, like other medicines, they may cause side effects and some are known to have significant potential to interact with other medicinal products. As a result, like any other medicine, herbal medicines should be used with care and experience with their use should be monitored. This is also why they are now covered by pharmaceutical legislation, which aims to protect public health by making sure that registered herbal medicines are safe and of good quality.

The IMB would like to take this opportunity to remind healthcare professionals to ask patients and carers about any use of and experience with herbal medicines, including any suspected side effects, which should in turn be notified to the IMB using the usual reporting options.

## Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

| Product | Safety Issue |
|---|---|
| **Strattera (atomoxetine)** | Risk of increased blood pressure and increased heart rate |
| **Torisel (temsirolimus)** | Advice regarding the need to visually inspect the diluent vial prior to mixing with Torisel concentrate to exclude the presence of particulate matter |
| **Rasilez (aliskiren)** | Potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease |
| **Velcade (bortezomib)** | Reminder that the correct administration procedure is via the intravenous route |
| **Dianeal, Extraneal and Nutrineal** | Notification relating to supply and the continued need to monitor dialysis patients for symptoms suggestive of aseptic peritonitis |
| **Gilenya (Fingolimod)** | Requirement for cardiovascular monitoring during treatment initiation |
| **Apidra (insulin glulisine)** | Supply issue |