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Patient Health Protection

**Monthly report**

**Issue number: 1112**

## Pharmacovigilance Working Party (PhVWP)

### December 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its December 2011 plenary meeting on 12-14 December 2011.

### Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy. The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States. For the publication policy, readers are referred to [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2009/10/WC500006181.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500006181.pdf).

The PhVWP also provides advice to the Committee for Medicinal Products for Human Use (CHMP) on centrally authorised products and products subject to ongoing CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the meeting highlights from the CHMP published under [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/landing/news\\_and\\_events.jsp&mid=](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=).

### ***Gonotropin-releasing hormone (GnRH) agonists – Risk of depression***

**Some evidence suggests that gonotropin-releasing hormone (GnRH) agonists are associated with an increased risk of depression, which may be severe, and their product information should be updated consistently across the EU.**

Following reports of severe depression including suicide from a Japanese survey and a further epidemiological study in the UK, the PhVWP conducted a review of gonotropin-releasing hormone (GnRH) agonists and the risk of depression. The PhVWP concluded that the risk of depression and

<sup>1</sup> Revision 1 introduces lovastatin in Footnote 3 and Annex 2 as part of the class-review of HMG-CoA reductase inhibitors – Risk of new onset diabetes as agreed by the PhVWP in March 2012 (see PhVWP Monthly Report March 2012).

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mood changes should be mentioned and warnings should be included, in a consistent manner and for all indications, in the product information of all medicinal products in the EU containing a GnRH agonist<sup>2</sup> (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

### ***HMG-CoA reductase inhibitors – Risk of new onset diabetes***

**HMG-CoA reductase inhibitors (statins) may increase the risk of new onset diabetes in patients already at risk of developing the disease. Patients at risk need monitoring; however the risk-benefit balance remains clearly positive.**

Following the publication of a meta-analysis which reported that therapy with HMG-CoA reductase inhibitors (statins) overall was associated with a slightly increased risk for the development of new onset diabetes (NOD), the PhVWP conducted a review of this risk based on all available data. The PhVWP concluded that HMG-CoA reductase inhibitors may increase the risk of NOD in patients already at risk of developing this disease, but that overall the risk-benefit balance remains clearly positive, given the benefit of HMG-CoA reductase inhibitors in reducing major cardiovascular events. A warning should therefore be included in the product information of all HMG-CoA reductase inhibitors authorised in the EU<sup>3</sup> aiming at monitoring of patients at risk (see Annex 2 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

The CHMP will be informed of the PhVWP recommendation with regard to the centrally authorised product PRAVAFENIX, containing pravastatin in combination with fenofibrate (for the latest product information see

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001243/human\\_med\\_001429.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001243/human_med_001429.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp)).

### ***Methotrexate – Risk of overdose due to erroneous daily intake of the weekly dose in rheumatologic and dermatologic indications***

**Product information for methotrexate for oral use in rheumatologic and dermatologic indications should emphasise that it should be taken once a week and patients should be informed of the risk of overdose due to erroneous daily intake of the intended weekly dose. Key elements for risk minimisation should be consistently reflected in product information across the EU to minimise the risk of inadvertent overdose.**

Given that cases of overdose, sometimes fatal, with methotrexate in rheumatologic and dermatologic indications due to erroneous daily instead of weekly intake have been reported in the EU, the PhVWP agreed to review how to further minimise the risk of medication errors. The PhVWP concluded that a simple message emphasising the need for adherence to once weekly intake in rheumatologic and dermatologic indications, and a consistent warning on the risk of overdose should be included in the summaries of product characteristics (SmPCs), the package leaflets (PLs) and the labelling of all

<sup>2</sup> The active substances included in this review were buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin.

<sup>3</sup> The active substances included in this review were atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

methotrexate-containing products for oral use authorised in the EU for these indications. The PhVWP further agreed that the question of whether to maintain the option of dividing the weekly dose should be decided at national level, and that additional risk minimisation measures may likewise be implemented at national level if considered appropriate (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the SmPCs, PLs and labelling, as well as practical information on implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

### ***Montelukast – Risk of psychiatric adverse reactions in children***

**Psychiatric and behaviour-related adverse reactions have been reported in patients treated with montelukast. The current knowledge in this respect is adequately reflected in the existing EU product information and safety monitoring will continue through routine pharmacovigilance activities.**

The PhVWP reviewed a risk management plan (RMP) for montelukast, submitted, as requested, by the originator marketing authorisation holder with regard to psychiatric adverse reactions in children following the assessment of the latest periodic safety update report (PSUR). The PhVWP concluded that the available information on psychiatric and behaviour-related adverse reactions are adequately reflected in the existing EU product information and that routine pharmacovigilance activities are adequate to continue monitoring this issue, for example in the framework of preparation and assessment of PSURs, taking into account future findings from ongoing research in children and adolescents (see Annex 4 for the Summary Assessment Report).

### ***Proton-pump inhibitors – Risk of hypomagnesaemia with long-term use***

**Proton-pump inhibitors (PPIs) may cause serious hypomagnesaemia and therefore for patients expected to be on prolonged treatment, especially when using other hypomagnesaemia-inducing medicines, healthcare professionals should consider measuring magnesium levels before and periodically during PPI treatment.**

Following case reports of serious hypomagnesaemia, the PhVWP conducted a review of this risk in association with proton-pump inhibitors (PPIs)<sup>4</sup> and concluded that the product information of all PPI-containing medicinal products authorised in the EU for long-term use should be updated, in particular to inform patients and healthcare professionals that PPIs may cause serious hypomagnesaemia and that therefore healthcare professionals should consider measuring magnesium levels before and periodically during treatment in patients where long term use is expected, and particularly those who concomitantly take other medicines that may cause hypomagnesaemia. The PhVWP also proposed communication on this safety concern to healthcare professionals at the level of Member States (see Annex 5 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

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<sup>4</sup> The active substances included in this review were dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

## **Guidelines and general matters**

Below is a summary of the main discussions on guidelines and other general matters of an organisational, regulatory or methodological nature.

### ***Work Plan for the CHMP Pharmacovigilance Working Party 2012***

The PhVWP noted that the CHMP, in November 2011, adopted the PhVWP work plan 2012 submitted by the PhVWP. In 2012, the PhVWP will continue focussing on the implementation of the new legislation (see PhVWP Monthly Report 1009), in addition to their continuous safety monitoring of medicines. For the work plan, interested readers are referred to the EMA website

([http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people\\_listing\\_000019.jsp&mid=WC0b01ac0580028d92&jisEnabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000019.jsp&mid=WC0b01ac0580028d92&jisEnabled=true)).

### ***CHMP Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In-vivo Clinical Use***

The PhVWP noted the release for public consultation of the draft CHMP Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In-vivo Clinical Use (EMA/CHMP/BMWP/86289/2010). This guideline was developed by the CHMP Blood Products Working Party (BMWP) with input from the PhVWP. Interested readers are referred to the agency's website

(<http://www.ema.europa.eu>).

## **Regulatory abbreviations**

CHMP – Committee for Medicinal Products for Human Use

CMDh – Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

EU – European Union

HMA – Heads of Medicines Agencies

PASS – post-authorisation safety study

PhVWP – CHMP Pharmacovigilance Working Party

PL – package leaflet

PSUR – periodic safety update report

RMP – risk management plan

SmPC – summary of product characteristics

## **Annex 1**

### ***Summary Assessment Report of the PhVWP December 2011***

## **Gonatotropin-releasing hormone (GnRH) agonists – Risk of depression**

### **Key message**

Some evidence suggests that gonatotropin-releasing hormone (GnRH) agonists are associated with an increased risk of depression, which may be severe, and their product information should be updated consistently across the EU.

### **Safety concern and reason for current safety review**

An increased risk of depression and depressive symptoms is known in patients treated with gonatotropin-releasing hormone (GnRH) agonists and is related to the reduction in oestrogen/testosterone levels.

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

The PhVWP agreed to carefully evaluate the new evidence of the increased risk caused by GnRH agonists, considering that depressive symptoms are already common in patients requiring treatment with GnRH agonists.

### **Clinical setting**

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

The GnRH agonists included in this review were buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin.

Patients with prostate cancer being treated with GnRH agonists are known to be at increased risk of developing depression or of a worsening of pre-existing depression. There is also a potential increased risk of mood changes and depression in females treated with GnRH agonists for non-cancer hormone-dependent conditions. Thoughts of death, suicidal ideation and suicide attempts are frequent complications of severe depression.

### **Information on the data assessed**

The data assessed in this review included data from the GPRD study and a previous assessment of the safety of leuprorelin based on a comprehensive review of the relevant literature [1-11] and spontaneous adverse reaction reports. Member States were also requested to provide information on the current product information for all GnRH agonists in their countries.

## Outcome of the assessment

The GPRD study showed a 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 endometriosis patients, the 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 prostate cancer patients, 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 suicide behaviour was observed in prostate cancer patients treated with GnRH agonists, but results should be interpreted with caution due to 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 of oestrogen/testosterone levels during treatment with GnRH agonists. Responses from the different Member States revealed the need for improved harmonised information on this risk in the product information of the whole class of GnRH agonists.

The PhVWP concluded that the risk of depression and mood changes should be mentioned, in consistent manner and for all indications, in the product information of all medicinal products in the EU containing a GnRH agonist, namely buserelin, goserelin, histrelin, leuprorelin, nafarelin or triptorelin.

The summaries of product characteristics (SmPCs) should include a warning that there is an increased risk of incident depression, which may be severe, in patients undergoing treatment with GnRH agonists and ask that patients are informed accordingly and treated as appropriate if symptoms occur. Also, mood changes and depression should be included in the SmPC section on undesirable effects with the frequency category "common" in long term use and "uncommon" in short term use. Higher frequencies may be appropriate for specific products and indications based on their own clinical trial and other data.

The package leaflets (PLs) should warn the patient that there have been reports of depression, in some cases severe, in patients taking the respective medicinal product and ask the patient to inform a physician in the case of depressed mood. The PL section on possible side effects should be in accordance with the SmPC.

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## **Annex 2**

### ***Summary Assessment Report of the PhVWP December 2011***

## **HMG-CoA reductase inhibitors – Risk of new onset diabetes**

### **Key message**

HMG-CoA reductase inhibitors (statins) may increase the risk of new onset diabetes in patients already at risk of developing the disease. Patients at risk need monitoring; however the risk-benefit balance remains clearly positive.

### **Safety concern and reason for current safety review**

Following the publication of a meta-analysis in 2010 [1] which reported that therapy with HMG-CoA reductase inhibitors overall was associated with a slightly increased risk for the development of new onset diabetes (NOD), the PhVWP agreed to conduct a review of this risk based on all the available data, both published and unpublished.

Since the publication of a trial in 2001 (WOSCOPS) [2], a number of clinical trials have examined the association between HMG-CoA reductase inhibitors and NOD. Although WOSCOPS [2] suggested a decreased risk for NOD, the JUPITER [3] and PROSPER [4] studies suggested an increased risk and the recent meta-analysis of 13 trials [1] reported that HMG-CoA reductase inhibitor treatment overall was associated with a slightly increased risk for the development of NOD (odds ratio 1.09; 95% CI 1.02-1.17). The authors calculated that this represented 1 additional case of diabetes per 1,000 person-years of treatment. Alternatively this could be expressed as 1 additional patient developing diabetes, who would not otherwise had done so, for every 255 patients treated for 4 years with a HMG-CoA reductase inhibitor.

### **Clinical setting**

HMG-CoA reductase inhibitors, commonly known as statins, are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) which controls the rate-limiting step in the cholesterol biosynthesis. These active substances are used to lower lipids in the blood.

There are differences between individual HMG-CoA reductase inhibitors in terms of both lipophilicity and potency, which may affect the ability of these substances to influence glucose homeostasis. However the two characteristics are not linked in that rosuvastatin is both hydrophilic and potent, pravastatin is hydrophilic but relatively less potent while atorvastatin is both lipophilic and potent.

HMG-CoA reductase inhibitors are one of the most widely prescribed classes of medicinal products in the EU, and prescribing is continuing to grow. Thus even a relatively small increase in the risk of NOD could potentially result in a significant number of additional cases of diabetes per year.

The active substances included in this review were atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

## Information on the data assessed

A list of questions was sent to the originator marketing authorisation holders for the concerned active substances in order to obtain all available data. Both non-clinical and clinical studies were assessed [1-130].

## Outcome of the assessment

The non-clinical studies provided important mechanistic information but their clinical relevance is limited by the difficulty in replicating risk factors for diabetes which clinically would develop over many years in animal models.

Comparison across different clinical studies and thus the class of HMG-CoA reductase inhibitors was limited by different patient populations, length of study and dose. As a result, stratification of patient population by risk factors may yield different conclusions to those drawn when considering the patient population as a whole. In addition for the majority of the trials, diabetes was not a predefined end point and therefore the method of diagnosis of diabetes differed between trials varying between physicians reporting only to documented biochemical analysis. Furthermore the frequency and time of analysis differed in that some trials relied on a single measurement of fasting blood glucose while others required two raised levels for the diagnosis of diabetes. Relatively few trials assessed HbA1c levels, a more long term, sensitive measure of glucose homeostasis.

All studies clearly demonstrated that the benefit of HMG-CoA reductase inhibitors in reducing major cardiovascular events is still maintained to a similar extent in patients developing NOD compared with those patients that do not. Set against the increased risk of 1 case of diabetes for every 255 patients treated with a HMG-CoA reductase inhibitors for 4 years, it was estimated that 5.4 deaths or myocardial infarctions could be avoided over that period in addition to the same number of strokes or coronary revascularisations. Hence the benefit in preventing total vascular events is approximately 9:1 in favour of the cardiovascular benefit. Thus the risk-benefit balance of these medicines remains clearly positive, including in those with diabetes or at risk of developing diabetes.

From the analysis of the non-clinical and clinical data, the PhVWP concluded that there is sufficient evidence to support a causal association between use of HMG-CoA reductase inhibitors and NOD. However the risk appears to be predominantly 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 delineate the at-risk population. Other risk factors include a history of hypertension, raised triglycerides and raised body mass index at baseline.

The evidence for a causal association is currently weakest for pravastatin where trials have suggested both an increased and decreased risk of NOD associated with therapy. However, given the critical influence the patient population plays in determining the risk of diabetes, there is currently insufficient data to exclude any HMG-CoA reductase inhibitor from the possibility of exacerbating the risk of NOD in a susceptible individual.

Despite the conclusion that the risk of NOD is increased in susceptible individuals, studies clearly demonstrate that the benefit of HMG-CoA reductase inhibitors in reducing major cardiovascular events is still maintained to a similar extent in this population. As a result the risk-benefit balance of these medicines remains clearly positive, including in those at risk of diabetes and with diabetes at baseline. However risk minimisation measures should be introduced in order to specify patients who are at risk, to identify the onset of NOD and to manage the condition appropriately.

Considering the above, the PhVWP concluded that a warning that HMG-CoA reductase inhibitors as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of

hyperglycaemia where formal diabetes care is appropriate should be included in the product information, i.e. the summaries of product characteristics (SmPCs) and the package leaflets, of all HMG-CoA reductase inhibitors authorised in the EU, namely medicinal products containing atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin. The warning should state that patients at risk (i.e. those with fasting glucose 5.6 - 6.9 mmol/L, body mass index > 30kg/m<sup>2</sup>, raised triglycerides or hypertension) should be monitored both clinically and biochemically according to national guidelines. In the undesirable effect sections of the product information, diabetes mellitus should be included as a common adverse reaction, supplemented in the SmPC with detailed data from the major studies.

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## **Annex 3**

### ***Summary Assessment Report of the PhVWP December 2011***

## **Methotrexate – Risk of overdose due to erroneous daily intake of the weekly dose in rheumatologic and dermatologic indications**

### **Key message**

Product information for methotrexate for oral use in rheumatologic and dermatologic indications should emphasise that it should be taken once a week and patients should be informed of the risk of overdose due to erroneous daily intake of the intended weekly dose. Key elements for risk minimisation should be consistently reflected in product information across the EU to minimise the risk of inadvertent overdose.

### **Safety concern and reason for current safety review**

Cases of overdose with methotrexate in rheumatologic and dermatologic indications were reported in the EU from January 2009 to August 2011 due to inadvertent daily instead of weekly intake, despite measures taken in most Member States to reduce this risk of error. In the reported cases, serious adverse reactions occurred, fatal in some cases, especially due to the haematological toxicity of methotrexate. The causes of errors in these cases range from prescribing and administration errors (mainly for hospitalised patients) to errors in self-administration (by patients at home, either inadvertently or by misunderstanding the medication schedule).

Given these cases, the PhVWP agreed to review how to further minimise the risk.

### **Clinical setting**

Oral use of methotrexate is indicated, inter alia, in the treatment of active rheumatoid arthritis and psoriasis in adults. The therapeutic anti-inflammatory effects of methotrexate appear to be related at least in part to interruption of adenosine and possible effects on tumour necrosis factors (TNF) pathways. The immunosuppressive and toxic effects of methotrexate are due to the inhibition of an enzyme involved in the metabolism of folic acid, dihydrofolate reductase.

### **Information on the data assessed**

The PhVWP assessed the case reports, further data from the marketing authorisation holders for methotrexate-containing products as well as information exchanged between Member States.

### **Outcome of the assessment**

Following the assessment of the case reports and further data from the marketing authorisation holders for methotrexate-containing products, an exchange of information between Member States showed that these medication errors had been reported in several Member States where risk minimisation measures had already been taken, such as communication with healthcare professionals, the use of a supportive prescribing system or amendments to the product information. It also showed that information on this risk in the product information differed substantively between Member States and sometimes between products in the same Member State.

In the light of these results and supported by the conclusions of two publications [1-2], the PhVWP agreed on key elements of a simple message emphasising the need for adherence to once weekly intake and a consistent warning on the risks of overdose (in particular the risks of haematological and gastrointestinal reactions) for inclusion in the summaries of product characteristics and package leaflets of all methotrexate-containing products for oral use authorised in the EU for rheumatologic and dermatologic indications, together with the statement "take the prescribed dose once a week" for printing on the package (labelling), preferably on the vial's cap if possible. The PhVWP further agreed that the question of whether to maintain the option of dividing the weekly dose should be decided at national level, and that additional risk minimisation measures may likewise be implemented at national level if considered appropriate.

## References

- [1] Oral methotrexate: preventing avoidable overdose. *Prescrire international*. 2007; 16: 150-152.
- [2] Blinova E, Volling J, Koczmarc C, Greenall J. Oral methotrexate: preventing inadvertent daily administration. *Can J Hosp Pharm*. 2008; 61: 275-277.

## **Annex 4**

### ***Summary Assessment Report of the PhVWP December 2011***

## **Montelukast – Risk of psychiatric adverse reactions in children**

### **Key message**

Psychiatric and behaviour-related adverse reactions have been reported in patients treated with montelukast. The current knowledge in this respect is adequately reflected in the existing EU product information and safety monitoring will continue through routine pharmacovigilance activities.

### **Safety concern and reason for current safety review**

Following the assessment of the periodic safety update report (PSUR) for montelukast covering the period from 31 July 2006 to 30 July 2009, case reports, received through spontaneous reporting schemes, on suspected psychiatric and behaviour-related adverse reactions were further evaluated. Based on this evaluation, the originator marketing authorisation holder was requested to submit a risk management plan (RMP) focusing on the main and most severe psychiatric adverse reactions reported in children. The draft RMP was scheduled for review by the PhVWP.

### **Clinical setting**

Montelukast is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene type-1 (CysLT1) receptor and is indicated for the treatment of asthma and allergic rhinitis.

### **Information on the data assessed**

The data assessed included the originator marketing authorisation holder's draft RMP focusing on the main and most severe behaviour-related adverse reactions in children.

### **Outcome of the assessment**

The PhVWP reviewed the RMP, and in particular whether the current risk management is sufficient or whether further pharmacovigilance activities or risk minimisation measures are warranted. The PhVWP concluded that the current EU product information is adequate in the light of the current knowledge and that the RMP should be finalised with the requirement to apply routine pharmacovigilance activities, including future PSURs, to closely monitor neuropsychiatric events and to give a summary evaluation in the next PSUR which is due later in 2012.

In this context, the PhVWP noted that a project focusing on suicidal adverse events associated with fluoxetine, risperidone and montelukast is being conducted by a group of experts in paediatric psychopharmacology within the framework of the European Child and Adolescent Paediatric Network (ECAPN), funded by the European Community's Seventh Framework Programme. The results of the project, which is anticipated to be completed in 2014, is expected to give further insight into the future evaluation of severe behavioural adverse events occurring in children treated with montelukast.

## **Annex 5**

### ***Summary Assessment Report of the PhVWP December 2011***

## **Proton-pump inhibitors – Risk of hypomagnesaemia with long-term use**

### **Key message**

Proton-pump inhibitors (PPIs) may cause serious hypomagnesaemia and therefore for patients expected to be on prolonged treatment, especially when using other hypomagnesaemia-inducing medicines, healthcare professionals should consider measuring magnesium levels before and periodically during PPI treatment.

### **Safety concern and reason for current safety review**

In March 2011, the Spanish competent authorities were made aware of a review by a regional pharmacovigilance centre in Spain investigating the risk of hypomagnesaemia in long-term users of proton-pump inhibitors (PPIs). The first case of hypomagnesaemia related to PPI intake was reported to that centre in 2008. An evaluation of all available data from spontaneous reporting in Spain, the published literature, the EudraVigilance database and other sources was performed in March 2011. A similar review had previously been carried out in the Netherlands, and additional information from the Dutch pharmacovigilance centre (Lareb) was also part of the Spanish assessment.

The PhVWP therefore agreed to conduct a review of this safety concern at EU level.

### **Clinical setting**

A large number of medicinal products containing a proton-pump inhibitor (PPI) are authorised and constitute one of the most widely used classes of medicines in the EU. The PPIs included in this review were dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

The mechanism of PPI-induced hypomagnesaemia is unknown, and several hypotheses have been postulated. A relevant aspect of this adverse effect is that patients usually have symptoms after using PPIs for three months or longer. Hypomagnesaemia means low blood magnesium levels. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur.

### **Information on the data assessed**

Case reports from spontaneous reporting schemes collected in the adverse reaction databases EudraVigilance and Vigibase (the database maintained by the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring) or reported in the medical literature [1-3] were assessed.

### **Outcome of the assessment**

The PhVWP considered that the case reports showed that most of the patients presented several hypomagnesaemia symptoms and hospitalisation episodes in previous years, which may reflect the difficulties on recognising this adverse reaction.

The PhVWP concluded that the product information of all PPI-containing medicinal products authorised in the EU for long-term use should inform patients and healthcare professionals of the rare but potentially serious risk of hypomagnesaemia associated with PPI intake. Although this adverse reaction may be rare, the wide use of PPIs, the seriousness of a number of cases of hypomagnesaemia and the lack of awareness of healthcare professionals, which may delay diagnosis and treatment, support this conclusion.

The PhVWP therefore recommended that section 4.4 of the summaries of product characteristics on warnings and precautions for use should inform healthcare professionals that

- severe hypomagnesaemia has been reported in patients treated with PPIs for at least three months, and in most cases for a year;
- serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but may begin insidiously and be overlooked;
- in most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI; and that
- for patients expected to be on prolonged treatment, and particularly those who take PPIs with digoxin or other medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment;

and that section 4.8 on undesirable effects should inform healthcare professionals that hypomagnesaemia may occur as an adverse reaction with unknown frequency.

The package leaflets should be updated accordingly and additionally ask the patient to inform a healthcare professional promptly, should any symptom of hypomagnesaemia occur.

In addition, the PhVWP proposed communication on this safety concern to healthcare professionals at the level of Member States. It was noted that the issue is already in the public domain after the publication of a number of case reports and recent public statements from several authorities.

## References

[1] Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med.* 2006; 355: 1834-1836.

[2] Cundy T, McKay JD. Proton pump inhibitors and severe hypomagnesaemia. *J Current Opinion in Gastroenterology.* 2011; 27: 180-185.

[3] Swaminathan K, Wilson J. Elusive cause of hypomagnesaemia. *Br Med J.* 2011; 343: d5087.