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Pharmacovigilance Working Party (PhVWP)

October 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its October 2011 plenary meeting on 17-19 October 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.

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/news/2011/10/news_detail_001360.jsp&mid=WC0b01ac058004d5c1

Antiepileptics – Risk of bone disorders

Long-term use of carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate is associated with a risk of decreased bone mineral density that may lead to osteopenia, osteoporosis and fractures.

The PhVWP concluded its class review of antiepileptics and risk of bone disorders including decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term treatment and recommended to include harmonised information in the summaries of product characteristics (SmPCs) and package leaflets (PLs) of all medicinal products in the EU containing carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine or sodium valproate.

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The PhVWP also agreed to keep this issue under review and recommended that marketing authorisation holders for all antiepileptics should be requested to consider any further cases of bone disorders and all future publications in the medical literature regarding antiepileptics and bone disorders in future periodic safety update reports (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Citalopram – Risk of QT interval prolongation

Citalopram may cause QT prolongation and the product information will be updated, in particular to reduce the maximum daily dose to 40mg/day in adults and 20 mg/day in the elderly and in patients with impaired liver function.

The PhVWP concluded its review of the antidepressant citalopram and the risk of QT prolongation with recommendations to update the summaries of product characteristics (SmPCs) and package leaflets (PLs) of citalopram-containing medicinal products in the EU (see Annex 2 for the Summary Assessment Report). The update should include reduction of the maximum daily dose to 40mg/day in adults and 20 mg/day in the elderly and in patients with impaired liver function, a contraindication against concomitant use with other medicines known to prolong the QT interval and a number of other contraindications and warnings.

The PhVWP informed the CMDh accordingly. For the final wording to be included in the SmPCs and 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.

Domperidone - Risk of cardiac disorders

Domperidone should be used at the lowest effective dose in adults and children because its use may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients older than 60 years or in patients taking daily doses of more than 30 mg.

Given new information from a published study, the PhVWP reviewed the risk of cardiac disorders associated with domperidone and concluded that the summaries of product characteristics (SmPCs) and package leaflets (PLs) of domperidone-containing products authorised in the EU should be modified in order to include information on the increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients older than 60 years or in patients taking daily doses of more than 30 mg, and in order to emphasise that domperidone should be used at the lowest effective dose in adults and children.

Further, the PhVWP recommended that the originator marketing authorisation holder should conduct an additional well-designed, high-powered epidemiological study to clarify the association between domperidone and cardiac disorders, with particular emphasis on dose relationship.

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

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.

ICH Implementation Guide (ICH-E2B(R3)) for the International Standard for the Electronic Transmission of Individual Case Safety Reports

The PhVWP noted that the ICH Implementation Guide ICH-E2B(R3) Step 3 was released by the CHMP for public consultation in the EU over the following 6 months. Interested readers are referred to the agency's website for upcoming information on the consultation.

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

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

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 October 2011

Antiepileptics – Risk of bone disorders

Key message

Long-term use of carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate is associated with risk of decreased bone mineral density that may lead to osteopenia, osteoporosis and fractures.

Safety concern and reason for current safety review

The causal association between the use of antiepileptic medicines such as carbamazepine, phenytoin, phenobarbital and primidone and the bone disorder osteomalacia is already known and is reflected in the product information for these medicines, albeit inconsistently. However, the causal association between antiepileptics and other bone disorders such as decreased bone mineral density, osteopenia and osteoporosis leading to fractures was not clear and, therefore, the PhVWP agreed to conduct a class review of antiepileptics and the risk of bone disorders.

Clinical setting

Osteomalacia is a condition affecting adults, where the bones become weak and softer than normal. With osteopenia, bone mineral density is lower than normal and this bone loss can develop into osteoporosis. Osteoporosis is a progressive systemic disease of the skeleton, characterised by reduced bone mass and density as well as micro-architectural deterioration of bone tissue. This leads to an increased bone fragility and susceptibility to fracture. Osteoporosis affects more than 50 million people worldwide [1]. More than 80% of fractures in people aged 60 years or older are osteoporosis-related [2].

Although there are many secondary risk factors for osteoporosis, an association between antiepileptics and osteoporosis would be of particular concern for elderly patients, who are already at risk of osteoporosis and who are likely to need antiepileptics because of the high prevalence of epilepsy in this age group. Furthermore, the use of antiepileptics in this age group extends beyond seizure management (e.g. for pain and psychiatric disorders).

Information on the data assessed

The review included clinical, non-clinical and epidemiological data published in the medical literature [3-41], and case reports of relevant suspected adverse reactions from spontaneous reporting schemes in the EU.

Outcome of the assessment

The PhVWP considered the following:

A large number of spontaneous case reports of bone disorders have been received for the active substances carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate. Although a number of risk factors were present in some of these cases, including the use of multiple antiepileptics, the use of other concomitant medicines known to cause bone disorders

and severe epilepsy that may contribute to fractures, there were several cases where additional risk factors did not appear to be present. In several cases, a causal association with use of these antiepileptics could not reasonably be excluded, particularly in cases where the antiepileptics were used for long time periods.

A number of published studies [3-41] provided evidence of an association between bone disorders and the following antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate. There were limitations to some of the published studies such as poor study design, small study population and lack of adjustments for potential confounders such as smoking status, level of physical activity, alcohol use and dietary calcium intake. A number of mechanisms by which antiepileptics may affect bone metabolism have been postulated in the medical literature but no single hypothesis fully explains the reported findings and it is possible that multiple mechanisms may be involved. Further investigations are warranted in this area.

Considering the above, the PhVWP concluded their class review with the recommendation to include harmonised information about the risk of bone disorders including decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term treatment in the summaries of product characteristics (SmPCs) and package leaflets (PLs) of all medicinal products in the EU containing carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine or sodium valproate. In the PL, patients should be made aware of the risk factors long-term treatment, history of osteoporosis and corticosteroid medication and be prompted to check with their healthcare professional.

The available data for the other antiepileptics was considered to be very limited and insufficient to support a causal association with bone disorders other than osteomalacia at present and no update of product information was required with respect to these products, some of which already include information on potential effects on bone.

The PhVWP also agreed to keep this issue under review and recommended that marketing authorisation holders for all antiepileptics should be requested to consider any further cases of bone disorders and all future publications in the medical literature regarding antiepileptics and bone disorders in the periodic safety update reports.

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Annex 2

Summary Assessment Report of the PhVWP October 2011

Citalopram – Risk of QT interval prolongation

Key message

Citalopram may cause QT prolongation and the product information will be updated, in particular to reduce the maximum daily dose to 40mg/day in adults and 20 mg/day in the elderly and patients with impaired liver function.

Safety concern and reason for current safety review

The PhVWP assessed new data from a randomised, multi-centre, double-blind, placebo-controlled, crossover pharmacokinetic and thorough QT-study undertaken in healthy volunteers given daily doses of 20 and 60 mg citalopram.

The FDA issued an announcement on 24 August 2011, notifying healthcare professionals in the US that citalopram should no longer be used at doses higher than 40 mg/day. The reason was identification of an increased risk for QT interval prolongation. As part of its review, the PhVWP assessed the data which formed the basis for this actionwhich included the results of the above mentioned study.

Clinical setting

Citalopram is indicated for the treatment for depression, panic disorder and obsessive-compulsive disorder (OCD).

QT interval prolongation is an indication of abnormal heart rhythm, which can lead to ventricular arrhythmia, including *torsade de pointes*, and sudden cardiac death.

Information on the data assessed

The PhVWP assessed the results of a randomised, multi-centre, double-blind, placebo-controlled, crossover pharmacokinetic and thorough QT-study undertaken in healthy volunteers given daily doses of 20 and 60 mg citalopram. The PhVWP additionally evaluated data from the marketing authorisation holder of the originator citalopram-containing product in the EU provided in response to a list of question from the PhVWP. Finally, spontaneously reported cases of suspected reactions which could be related to QT interval prolongation were reviewed.

Outcome of the assessment

Following review of the thorough QT-study, the following can be concluded: A dose-dependent increase in QT interval was shown in this thorough QT study, particularly with 60 mg/day.The change from baseline in QTc (Fridericia-correction) was 7.5 (90%CI 5.9-9.1) msec with 20 mg/day and 16.7 (90%CI 15.0-18.4) msec with 60 mg day. The study was considered of good quality, although testing of a higher dose would have been desirable (in accordance with the ICH E14 guideline). A positive control was included, i.e. moxifloxacin 400 mg/day, which showed expected results, thus confirming assay sensitivity.

Further, the PhVWP considered that cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes were spontaneously reported, predominantly in female patients, with hypokalemia, pre-existing QT interval prolongation or other cardiac diseases. Most of the reported cases of torsade de pointes had a positive dechallenge. Positive rechallenge was also reported. In addition, a number of cases of ventricular arrhythmia, sudden death, loss of consciousness and syncope might also be associated with torsade de pointes. The data from spontaneous reporting also had limitations, for instance underreporting was considered as potentially large for events such as torsades de pointes, cardiac arrhythmia or sudden cardiac death. Thus, those data could not be used to exclude the existence of a risk.

Overall, the PhVWP considered that the results from the study indicated that citalopram causes dose-dependent QT interval prolongation. In considering the appropriate risk minimisation strategy, the PhVWP also noted that elderly patients and patients with reduced liver function achieve higher systemic exposure than younger patients with normal hepatic function. Furthermore, it was also noted that cases of QT-interval prolongation have been reported also in association with some other selective serotonin re-uptake inhibitors (SSRIs) including escitalopram, the S-enantiomer of citalopram.

Based on a review of the available data, the PhVWP concluded that the summary of product information for citalopram-containing medicinal products in the EU should be updated to

- remove the dose recommendation of 60 mg/day;
- limit the maximum daily dose for adults to 40 mg/day;
- limit the daily dose in the elderly and in patients with hepatic impairment to 20 mg/day;
- contraindicate use of citalopram with other medicinal products known to prolong the QT interval;
- include relevant contraindications and warnings; and
- include ventricular arrhythmia including torsade de pointes as adverse reactions.

The package leaflet should be updated accordingly and include advice to patients to

- contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram;
- not to stop taking citalopram or change or reduce the dose without first consulting their healthcare professional, as withdrawal symptoms may occur when citalopram treatment is discontinued, particularly if this is abrupt;

Healthcare professionals are advised to review patients on doses that are above the now recommended maximum dose and gradually reduce the dose accordingly.

Annex 3

Summary Assessment Report of the PhVWP October 2011

Domperidone - Risk of cardiac disorders

Key message

Domperidone should be used at the lowest effective dose in adults and children because of its use may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients older than 60 years or in patients taking daily doses of more than 30 mg.

Safety concern and reason for current safety review

Although in 2008, the sections 4.4, 4.5 and 4.8 of the summaries of product characteristics of domperidone-containing products authorised in the EU were updated to include additional information on the risk of QT interval prolongation, the need for additional regulatory action would have been considered needed in light of new data.

In 2010 the results of a study [1] suggested that the current use of domperidone, especially at high doses, suggested an association with an increased risk of ventricular arrhythmia and sudden cardiac death. The authors could not demonstrate an effect of domperidone on non-fatal ventricular arrhythmia due to the absence of exposed cases. The PhVWP therefore agreed to assess the concern about the risk of sudden cardiac death with domperidone, particularly at high doses or in patient older than 60 years.

Clinical setting

Domperidone is a propulsive agent and a dopamine antagonist with antiemetic properties. It is widely used and available on prescription only or without prescription, depending on the Member State, and administrated via the oral or rectal route. In the EU Member States, domperidone is authorised in adults for the relief of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents, and in children for the relief of nausea and vomiting.

QT interval prolongation is an indication of abnormal heart rhythm, which can lead to ventricular arrhythmia, including *torsade de pointes*, and sudden cardiac death.

Information on the data assessed

A cumulative review of relevant case reports from spontaneous reporting was provided by the originator marketing authorisation holder. The overall exposure worldwide has been estimated at 1.3 billion treatment courses for over 30 years. In these reports, no cases of sudden cardiac death without another risk factor were identified. The limited data provided in these reports preclude differentiation between short and long-term use or between use with or without prescription. The reports do not also allow for an evaluation of the effect of total daily doses or patient age on the reporting of serious ventricular arrhythmia and sudden cardiac death.

A search in the Eudravigilance database was performed by the agency and the cases retrieved showed a potential association between domperidone and QT interval prolongation for non-parenteral routes of administration and an association with *torsade de pointes* independently of the route.

Four epidemiological studies from independent databases have reported on the relationship between domperidone and either sudden cardiac death alone or serious ventricular arrhythmia and sudden cardiac death as a combined endpoint.

Outcome of the assessment

Based on the information assessed, the PhVWP concluded that modifications to the summaries of product characteristics and package leaflets of domperidone-containing products authorised in the EU are necessary in order to include the risk of sudden cardiac death, particularly in patients older than 60 years and in patients taking daily doses of more than 30 mg, and in order to emphasise that domperidone should be used at the lowest effective dose in adults and children.

Further, the PhVWP recommended that the originator marketing authorisation holder should conduct an additional well-designed, high-powered epidemiological study on the association between domperidone and cardiac disorders, with particular emphasis on dose relationships.

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