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Pharmacovigilance Working Party (PhVWP)

July 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its July 2011 plenary meeting on 18-20 July 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 CHMP monthly report (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000190.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028d2a).

Antipsychotics – Risk of extrapyramidal effects and withdrawal symptoms in newborns after exposure during pregnancy

Extrapyramidal effects and withdrawal symptoms may occur in newborns after exposure to antipsychotics during the third trimester of pregnancy, and product information across the EU should contain consistent information.

The PhVWP reviewed new data from worldwide spontaneous reporting and information made available to the Agency by the US Food and Drug Administration (FDA) on neonatal withdrawal syndrome and extrapyramidal effects in newborns in association with antipsychotics and its implications for the content of the summaries of product characteristics (SmPCs) and package leaflets (PLs) of those

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products authorised in the EU[1]. The PhVWP concluded that the available data indicate a risk of extrapyramidal effects and of withdrawal symptoms in newborns following maternal use of antipsychotics during the third trimester of pregnancy and agreed core information to be included in the SmPCs and PLs for all antipsychotics in the EU (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the final core information 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.

Fusidic acid – Risk of rhabdomyolysis due to interaction with HMG-CoA reductase inhibitors

In patients needing systemic treatment with fusidic acid the use of statins (HMG-CoA reductase inhibitors) should be interrupted, and patients using fusidic acid should seek immediate medical advice for symptoms such as muscle weakness, pain or tenderness.

The PhVWP conducted a review of new cases from spontaneous reporting and the medical literature on the risk of rhabdomyolysis associated with concomitant use of fusidic acid and HMG-CoA reductase inhibitors[2]. The PhVWP concluded the review with the recommendation that a minimum warning against concomitant use with HMG-CoA reductase inhibitors, including detailed advice on discontinuation and reintroduction of HMG-CoA reductase inhibitor treatment, should be added to the product information of fusidic acid-containing medicinal products for systemic use (see Annex 2 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the final minimum wordings to be included in the summary 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.

Plantago ovata (syn.: P. isphagula) – Risk of allergic reactions after prolonged occupational exposure

Healthcare professionals, caregivers and pharmaceutical industry workers should be aware of the risk of allergic reactions after prolonged occupational exposure to the powder of Plantago ovata seed products and stop current and future exposure in the case of proven allergic sensitisation.

Following case reports and study results from Spain, the PhVWP concluded their review of the available data on the risk of allergic reactions of Plantago ovata-containing products in persons preparing these laxatives for administration to patients. The PhVWP concluded that the product information of Plantago ovata seed-containing medicinal products as powder formulations should be updated to include the risk of allergic reactions after prolonged occupational exposure and the warning to stop current exposure and avoid future exposure to these products in the case of proven allergic sensitisation (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the final wordings 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.

[1] The active substances included in the review were chlorpromazine, clotiapine, clozapine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, risperidone, thioridazine, thiothixene, trifluoperazine and ziprasidone.
[2] This includes the following active substances: atorvastatin, cerivastatin (marketing authorisation withdrawn), fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin.

The PhVWP also informed the Committee on Herbal Medicinal Products of this review, and for updates of the corresponding Community Herbal Monographs, interested readers are advised to consult the Agency website (http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fdocument_library%2Flanding%2Fdocument_library_search.jsp&murl, filter by document type: Herbal – Community herbal monograph)

Reboxetine – Confirmation of positive benefit-risk balance

The PhVWP review confirms the safety and efficacy of reboxetine in the treatment of depressive illness and major depression and in maintenance therapy.

A meta-analysis, conducted as part of a health technology assessment of three antidepressants by the German institute IQWiG, was published in the British Medical Journal in November 2010, questioning the positive benefit-risk balance of reboxetine.

The PhVWP therefore reviewed the meta-analysis as well as all other available data and concluded that the benefit-risk balance of reboxetine when used in accordance with its currently authorised indications remains positive. Reboxetine is authorised for the acute treatment of depressive illness and major depression and for maintaining clinical improvement in patients initially responding to treatment. Given the interest that has been stimulated by the publication of the meta-analysis, the PhVWP recommended that healthcare professionals should receive communication at the level of Member States to explain the reasons why the regulatory position remains unchanged (see Annex 4 for the Summary Assessment Report).

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.

EudraVigilance Access Policy for Medicines for Human Use

The PhVWP noted that the EudraVigilance Access Policy for Medicines for Human Use (see www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf) was published by the Agency on 8 July 2011. The PhVWP had been consulted during the development of this policy.

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMD(h) – 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 July 2011

Antipsychotics – Risk of extrapyramidal effects and withdrawal symptoms in newborns after exposure during pregnancy

Key message

Extrapyramidal effects and withdrawal symptoms may occur in newborns after exposure to antipsychotics during the third trimester of pregnancy, and product information across the EU should contain consistent information.

Safety concern and reason for current safety review

Following new data from worldwide spontaneous reporting and information made available to the Agency by the US Food and Drug Administration (FDA) on neonatal withdrawal syndrome and extrapyramidal effects in newborns in association with antipsychotics, the PhVWP agreed to review the implications of this new information for the content of the summaries of product characteristics (SmPCs) and package leaflets (PLs) of those products authorised in the EU.

The active substances included in the review were chlorpromazine, clotiapine, clozapine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, risperidone, thioridazine, thiothixene, trifluoperazine and ziprasidone.

Clinical setting

Antipsychotics are medicines used for some types of mental distress or disorder.

Information on the data assessed

The PhVWP reviewed data from worldwide spontaneous reporting and information made available to the Agency by the US Food and Drug Administration (FDA) [1] on neonatal withdrawal syndrome and extrapyramidal effects in newborns in association with antipsychotics.

A review of the SmPCs of the antipsychotics authorised in the EU showed inconsistencies between the SmPCs in the information provided in section 4.6 on fertility, pregnancy and lactation about the possible effects on the newborn following maternal use during the third trimester of pregnancy. In many cases, this information was absent from the SmPCs.

At the same time, the marketing authorisation holder for the centrally authorised medicinal products containing the antipsychotic paliperidone (INVEGA and XEPLION) had submitted a variation application to update section 4.6 of the SmPC to include the risks of extrapyramidal effects and withdrawal symptoms in response to the action taken in the US. The assessment of the application concluded that there was a risk of extrapyramidal effects and of withdrawal symptoms in newborns following maternal use of paliperidone during the third trimester of pregnancy and recommended including these risks in SmPC section 4.6 and section 4.8 on undesirable effects and in the corresponding sections of the PLs.

Outcome of the assessment

Although the data was limited for some antipsychotics with regards to effects in newborns following maternal use during pregnancy, the PhVWP agreed that these effects are likely to be a class effect and considered that the wordings in the product information should be consistent for the whole class of antipsychotics.

The PhVWP subsequently concluded that there was a risk of extrapyramidal effects and withdrawal symptoms in newborns following maternal use of antipsychotics during the third trimester of pregnancy and agreed core information to be included for the SmPCs and PLs for all antipsychotics in the EU (i.e. chlorpromazine, clotiapine, clozapine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, risperidone, thioridazine, thiothixene, trifluoperazine and ziprasidone). The wordings of the core information are consistent with the wordings already agreed for paliperidone and the FDA approved drug labels.

References

[1] U.S. Food and Drug Administration. FDA Drug Safety Communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. Silver Spring, MD: US FDA; 22 February 2011.

Annex 2

Summary Assessment Report of the PhVWP July 2011

Fusidic acid – Risk of rhabdomyolysis due to interaction with HMG-CoA reductase inhibitors

Key message

In patients needing systemic treatment with fusidic acid the use of statins (HMG-CoA reductase inhibitors) should be interrupted, and patients using fusidic acid should seek immediate medical advice for symptoms such as muscle weakness, pain or tenderness.

Safety concern and reason for current safety review

Variation applications proposing to contraindicate concomitant use of systemic fusidic acid with all HMG-CoA reductase inhibitors due to the associated risk of rhabdomyolysis had been submitted by the marketing authorisation holder for systemic fusidic acid in a number of Member States.

This referred to an interaction which was already known and included as a warning in the product information for systemic fusidic acid and the HMG-CoA reductase inhibitors simvastatin and atorvastatin. The newly arising signal, based on spontaneous case reports and literature case reports, concerned an increase in the number and severity of cases of rhabdomyolysis reported, including several with fatal outcome.

Clinical setting

Fusidic acid is an active substance against staphylococcal infections and is used relatively infrequently systemically, when compared to other anti-staphylococcal substances. It is most usually chosen for the treatment of serious or deep-seated staphylococcal infections requiring good tissue or bone penetration (e.g. osteomyelitis), and its use is usually guided by in-vitro tests confirming susceptibility. For such infections, it is commonly used orally and almost always in combination with another anti-staphylococcal substance in order to avoid the rapid development of fusidic acid resistance in-vivo during the treatment course. In the context of infections with methicillin-resistant Staphylococcus aureus (MRSA), it is frequently one of only a very small number of active substances available for therapy if in-vitro susceptibility tests confirm fusidic acid susceptibility.

Important aspects of the substance

The specific pathways of the metabolism of fusidic acid in the liver are not known; it is excreted mainly in the bile, and little or none being excreted in the urine. The exact mechanisms of the interaction between fusidic acid and HMG-CoA reductase inhibitors are currently also unclear. This may include pharmacodynamic or pharmacokinetic mechanisms, or a combination of both. It is of note that different HMG-CoA reductase inhibitors are metabolised to a variable extent and also have different pathways of hepatic metabolism.

Information on the data assessed

The data provided by the marketing authorisation holder to support the variation application was based on spontaneously reported cases and case reports published in the medical literature.

Outcome of the assessment

The PhVWP considered that the available data might be limited by several issues, such as under-reporting and the fairly small number of reported cases. Nevertheless, the use of fusidic acid is quite low and therefore the number of cases received was considered significant. The quality and quantity of the detail provided for each case report was variable which made comparison between cases difficult. In many of the cases the patients involved also had complex medical problems and were receiving multiple concomitant medications.

Despite the additional limitations of data on the exact mechanisms of the interaction between fusidic acid and HMG-CoA reductase inhibitors, the PhVWP agreed that the risk of this potentially serious interaction and subsequent rhabdomyolysis needed to be adequately addressed in the product information. The PhVWP discussed whether a contraindication of concomitant use of systemic fusidic acid and HMG-CoA reductase inhibitors would restrict the use of fusidic acid in cases where this may be the only and last remaining treatment option available for serious staphylococcal infections. The PhVWP noted that some Member States had already implemented a contraindication. The PhVWP agreed that national treatment guidelines might differ in relation to the use of fusidic acid and therefore some flexibility in the product information would be appropriate.

The PhVWP concluded upon a minimum warning against concomitant use with HMG-CoA reductase inhibitors, including detailed advice on discontinuation and reintroduction of HMG-CoA reductase inhibitors treatment, to be added to the product information of fusidic acid-containing medicinal products for systemic use.

The PhVWP agreed upon the advice that there should be an interval of 7 days after the last dose of fusidic acid before commencing an HMG-CoA reductase inhibitor. Although the half-life of fusidic acid in serum is short, at present there are no data on how long the hepatic intracellular concentrations of fusidic acid persist. Therefore, the PhVWP recommended a conservative period of 7 days to further minimise the possibility of interaction between any residual intracellular fusidic acid with HMG-CoA reductase inhibitors.

The warning should also emphasise the importance of seeking medical advice immediately for early symptoms of muscle weakness, pain or tenderness in order to further minimise risk. This message should be clearly communicated in the package leaflet.

As the mechanisms of the interaction remain unknown, the warning should apply to any HMG-CoA reductase inhibitor, i.e. atorvastatin, cerivastatin (marketing authorisation withdrawn), fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin.

References

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[2] Burtenshaw AJ, Sellors G, Downing R. Presumed interaction of fusidic acid with simvastatin. Anaesthesia. 2008; 63: 656-658.

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Annex 3

Summary Assessment Report of the PhVWP July 2011

Plantago ovata (syn.: P. isphagula) – Risk of allergic reactions after prolonged occupational exposure

Key message

Healthcare professionals, caregivers and pharmaceutical industry workers should be aware of the risk of allergic reactions after prolonged occupational exposure to the powder of Plantago ovata seed products and stop current and future exposure in the case of proven allergic sensitisation.

Safety concern and reason for current safety review

The Spanish competent authorities informed the PhVWP of 31 case reports of allergic reactions associated with powder formulations of Plantago ovata seeds received through the Spanish pharmacovigilance reporting system. Most of these cases (25) were reported recently in healthcare professionals who unintentionally inhaled the seed powder who had been handling these products for years while preparing them for administration to patients. These individuals predominantly presented respiratory symptoms (rhinitis, asthma), severe in some persons, shortly after inhalation of the powder.

According to the results of a study performed in Spain [1] in a sample of healthcare professionals in geriatric care homes who had been repeatedly exposed to Plantago ovata seed products, about 9% of healthcare professionals suffered allergic reactions confirmed by allergy tests.

Plantago ovata seed-containing products are available as powder or as granules for oral use. The safety concern is related to the inhalation of the product in powder formulation, since the particles in this formulation, before dissolution in water, are sufficiently small to become airborne and reach the airways.

The PhVWP agreed to review this safety concern.

Clinical setting

Plantago ovata (synonym: P. isphagula) is a plant, and as herbal medicinal product it is used as a bulk laxative against constipation. The active ingredients of Plantago ovata are the mucilages located in the husk of the seed [2, 3].

Chronic constipation is very common in the elderly population, and Plantago ovata has been widely used as laxative in this population for many years. In elderly care homes in Spain, powder formulations are commonly used and healthcare professionals and caregivers are exposed to it on a daily basis when preparing these formulations for administration.

Information on the data assessed

A number of well documented case reports from Spain and other Member States and some studies performed in different settings and countries [1, 4-10] were assessed.

Outcome of the assessment

The PhVWP considered that the studies published in the past in different countries [4-10] show results similar to the recent Spanish study [1]. In addition, cases have been reported in pharmaceutical industry workers manipulating the seeds during the manufacturing which are also similar to the cases in healthcare professionals.

On the other hand, the PhVWP considered that, although these products are available in most Member States of the EU, only a limited number of cases of allergic reactions have been reported in patients using Plantago ovata, and most of them were non-serious.

Based on the review of the data, the PhVWP concluded that allergic symptoms, confirmed by allergic tests, were present in a significant proportion (around 9%) of persons with prolonged occupational exposure to Plantago ovata seed powder. Some cases were serious (asthma, anaphylactic reactions with hypotension). Persons with atopy (i.e. genetic tendency to develop allergies involving the capacity to produce IgE in response to common environmental proteins) were considered to be at increased risk. As with other allergic reactions, avoiding exposure to the causal agent (by inhalation or ingestion) is the best way to prevent the adverse events in the sensitised population.

The PhVWP considered it relevant to increase the awareness of the risk of allergic reactions associated with Plantago ovata seed-containing products as powder formulations in healthcare professionals, caregivers and workers in the pharmaceutical industry and to warn them that stopping exposure is needed and that future exposure to these products is to be avoided in the case of proven allergic sensitisation. The summaries of products characteristics and package leaflets of these products should be updated to include this information.

References

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Annex 4

Summary Assessment Report of the PhVWP July 2011

Reboxetine – Confirmation of positive benefit-risk balance

Key message

The PhVWP review confirms the safety and efficacy of reboxetine in the treatment of depressive illness and major depression and in maintenance therapy.

Safety concern and reason for current safety review

A meta-analysis investigating the impact of possible publication bias on the overall evaluation of the safety and efficacy of reboxetine was published in the British Medical Journal in November 2010 [1]. The study was conducted as part of the health technology assessment of three antidepressants by the German Institute for Quality and Efficiency in Health Care/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) [2] and concluded that reboxetine was 'an ineffective and potentially harmful antidepressant' [1].

As a result of the concerns raised, the PhVWP agreed to review the totality of safety and efficacy data for reboxetine to consider whether any changes to the marketing authorisation of reboxetine were required.

Clinical setting

Reboxetine is a selective noradrenaline reuptake inhibitor, the only member of this particular pharmacological class of medicines. It was authorised in the European Union in 1996 for the acute treatment of depressive illness/major depression and for maintaining clinical improvement in patients initially responding to treatment.

Information on the data assessed

The PhVWP reviewed data from the meta-analysis, which included 13 acute treatment trials (placebo controlled, selective serotonin reuptake inhibitor (SSRI) controlled, or both) involving 4098 patients [1, 2]. Data on 74% (3033 out of 4098) of these patients were unpublished.

In addition, the PhVWP reviewed all the data from the original marketing authorisation application, along with the responses from the marketing authorisation holder to a detailed list of questions on safety and efficacy designed to capture all clinical trial data and to explore reasons for the differences between the studies conducted in the pre- and post-authorisation phases.

Outcome of the assessment

For the meta-analysis [1], the PhVWP noted that for the analysis of remission rates, which included seven trials, no significant difference compared with placebo was shown (OR 1.17, 95% CI 0.91 to 1.51; P=0.216).

It was further noted that eight trials investigated response rates for reboxetine versus placebo. This analysis showed no significant difference in response rates between patients receiving reboxetine and those receiving placebo (OR 1.24, 95% CI 0.98 to 1.56; P=0.071).

The PhVWP considered that the meta-analysis had methodological limitations. A pivotal efficacy study was excluded in the efficacy analysis but included in the safety assessment based on the positive efficacy result being regarded as a statistical outlier; this was not considered an adequate justification for omitting a valid study.

When data from this study and other earlier studies that formed part of the original marketing authorisation application were included in a meta-analysis performed by the marketing authorisation holder, reboxetine showed a benefit over placebo in the treatment of depression.

In reviewing the totality of data, the PhVWP noted that there was a clear distinction between results obtained from studies conducted before 1996 and those conducted after the EU marketing authorisation, which were submitted to satisfy the request from the US Food and Drug Administration (FDA) for data from the US. The two sets of studies differed not only in time period but also by geographical location, baseline disease severity and care setting.

The PhVWP considered that care setting and baseline disease severity may be the most likely explanations for the difference in size of the reboxetine treatment effect between studies conducted in the pre- and post-authorisation phase. Studies in an in-patient setting and in severe depression consistently showed better efficacy results than studies conducted in out-patients. The greater effect compared with placebo seen in more severely depressed patients is also seen with other antidepressants and this finding fits well with current clinical guidance that antidepressants are not recommended for the first line treatment of mild or moderate depression.

A thorough review of all available safety data has not identified any previously unrecognised safety concerns associated with reboxetine and has confirmed the adverse reaction profile previously recognised.

The PhVWP concluded that the positive benefit-risk balance of reboxetine when used in accordance with its currently authorised indications remains unchanged. It was agreed that it would be appropriate to propose an amendment to section 5.1 of the summary of product characteristics that reflects the limitations of the data supporting the clinical efficacy in patients with mild to moderate depression.

Given the interest that has been stimulated by the publication in the British Medical Journal, the PhVWP recommended that healthcare professionals should receive communication at the level of Member States to explain the reasons why the regulatory position remains unchanged and to highlight the distinct findings in the studies conducted in the pre- and post-authorisation phases.

References

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