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MONTHLY REPORT

PHARMACOVIGILANCE WORKING PARTY (PHVWP)

OCTOBER 2009 PLENARY MEETING

The CHMP Pharmacovigilance Working Party (PhVWP) held its October 2009 plenary meeting on 19-21 October 2009.

PhVWP DISCUSSIONS ON SAFETY CONCERNS

Below is a summary of the discussions regarding non-centrally authorised medicinal products in accordance with the PhVWP publication policy (see under http://www.emea.europa.eu/htms/human/phv/reports.htm). Positions agreed by the PhVWP for non-centrally authorised products are recommendations to Member States.

For safety updates concerning centrally authorised products and products subject to ongoing CHMP procedures, readers are referred to the CHMP Monthly Report (see under http://www.emea.europa.eu/pressoffice/presshome.htm). The PhVWP provides advice on these products to the Committee of Medicinal Products for Human Use (CHMP) upon its request.

Antipsychotics - risk of venous thromboembolism (VTE)

Identify risk factors for VTE for preventive action before and during treatment with antipsychotics

The PhVWP completed their review on the risk of VTE of antipsychotics[1].

The review was triggered by and based on data from the UK spontaneous adverse drug reactions reporting system and the published literature. The PhVWP carefully considered the data, including the limitations of both information sources, such as the lack of randomised controlled trial data, the heterogeneity of published studies and the potential confounding factors such as sedation and weight gain, commonly present in antipsychotic users. The PhVWP concluded that an association between VTE and antipsychotics cannot be excluded. Distinguishing different risk levels between the various active substances was not possible.

[1] The recommendation of the PhVWP covers the following active substances: acepromazine, amisulpiride, benperidol, bromoperidol, chlorpromazine, chlorprothixene, clotiapine, clozapine, cyamemazine, dixyrazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, loxapine, melperone, penfluridole, pericyazine, perphenazine, pimozide, pipamerone, pipothiazine, prochlorperazine, promazine, prothipendyl, quetiapine, risperidone, sertindole, sulpiride, tiapride, trifluoperazine, ziprasidone, zotepine and zuclopenthixol.

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As a result of their review, the PhVWP recommended that the product information should state that cases of VTE (including pulmonary embolism and deep vein thrombosis) have been reported with antipsychotic medicines, that risk factors for VTE should be identified before and during treatment and appropriate preventive measures should be taken.

The PhVWP informed the CMD(h) accordingly, and for the final wordings to be included in the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) as well as practical information on the implementation, interested readers are asked to visit the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

There are also centrally authorised antipsychotics containing aripiprazole, olanzapine and paliperidone. For information on these products, readers are referred to the EMEA website (http://www.emea.europa.eu/).

Finasteride - risk of male breast cancer

Patients should be instructed to promptly report any changes in breast tissue to physicians.

The PhVWP conducted a review on the risk of breast cancer in men taking different strengths of finasteride, following case reports and in light of the biologically plausible mechanism.

A formulation containing 1mg of finasteride is used for male pattern hair loss. The majority of reports from clinical trials and the post-marketing case reports have been in association with the use of the 5mg formulation but there have been a small number of cases reported post marketing, in association with the 1mg formulation. The PhVWP recognised the limitations of the available data but considered that it could not rule out that there was a weak signal of an increased risk of male breast cancer associated with finasteride and that the product information should be updated to reflect the reported cases. The PhVWP also considered the proposals that had been made by the Marketing Authorisation Holder to further evaluate this issue.

Given the available data, the PhVWP recommended that prescribers are aware of these findings and patients using finasteride 1 or 5 mg are instructed to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia (enlargement of the male breast tissue) or nipple discharge.

This review was completed within the scheme for worksharing between Member States for the assessment of periodic safety update reports (see PhVWP Monthly Report 0909) and the implementation of the recommendations above will be processed as defined by the procedures developed for this scheme. For upcoming information regarding the implementation of the recommendations, interested readers are asked to visit the HMA website (http://www.hma.eu/80.html).

Short-acting beta agonists (SABAs) - Risk of myocardial ischaemia

Warn patients with severe heart disease using SABAs in respiratory diseases to seek medical advice in case of symptoms of worsening heart disease. In pregnant women with or at increased risk for heart disease, do not use SABAs[2] to inhibit uterine contractions.

Salbutamol is a short-acting β_2-adrenoceptor agonist and it is used as a sympathomimetic agent for the management of asthma, bronchospasm and/or reversible airways obstruction as well as in the management of premature labour. Previously, the PhVWP had reviewed data suggestive of a possible association between the use of inhaled and intravenous salbutamol and myocardial ischaemia.

The review included data from clinical trials, published epidemiological studies, other publications, spontaneous reports and analyses of disproportionate reporting. Based on this evidence, the PhVWP recommended the following changes to the product information: the use of salbutamol to inhibit uterine contractions is contraindicated in women with pre-existing ischaemic heart disease or with significant risk factors for ischaemic heart disease; when used in respiratory disease, for patients with

[2] The review covered the following active substances: bambuterol, clenbuterol, ephedrine, fenoterol, hexoprenaline, orciprenaline, pirbuterol, procaterol, reproterol, ritodrine, terbutaline and tolbuterol relating to respiratory and obstetric indications

severe underlying heart disease, consideration should be given to monitor cardiorespiratory function and patients should be warned to seek medical advice in case of symptoms of worsening heart disease.

Given their pharmacological properties, the PhVWP considered that there is a biological plausibility that all SABAs may potentially increase the risk of myocardial ischaemia. Therefore, the PhVWP concluded that the product information of all SABAs should include contraindications and warnings regarding the risk of myocardial ischaemia similar to those for salbutamol. The PhVWP informed the CMD(h) accordingly, and for the final wordings to be included in the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs), interested readers are asked to visit the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Zanamivir – Death of a patient after off-label use (nebulisation) of RELENZA inhalation powder

The PhVWP noted that in some Member States the marketing authorisation holder informed healthcare professionals directly by means of a Direct Healthcare Professional Communication and has contacted the other Member States, reminding that Relenza (zanamivir) inhalation powder must not be nebulised. A patient with influenza, unable to take oral medications or actively inhale a medication, died after receiving Relenza obtained by disolving the inhalation powder for use in a ventilator. This formulation is not designed or intended to be administered by nebulisation. There is risk that the lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment.

GUIDELINES AND GENERAL MATTERS

Below readers will find a summary of the principal discussions on guidelines and other general matters of organisational, regulatory or methodological nature.

Pharmacovigilance for medicinal products used against novel swine-origin Influenza A (H1N1) virus in humans

Medicines used to treat or prevent influenza belong to the group of antivirals and vaccines. The EMEA is engaged, in close co-operation with European and international partners, in ensuring the availability and surveillance of medicines effective against the pandemic A (H1N1) influenza. The PhVWP supports the activities undertaken by the EMEA in this respect. These activities are reported to the public via the EMEA website under http://www.emea.europa.eu/htms/human/pandemicinfluenza/novelflu.htm.

Medical Dictionary for Drug Regulatory Activities (MedDRA) - Preparation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Meetings in October 2009

In preparation of the next meetings of the ICH, the PhVWP provided feedback to the European Commission services in relation to the maintenance and further development of MedDRA. MedDRA is a dictionary of medical terms which has been developed within the processes of ICH. ICH develops guidelines applicable in the European Union, Japan and the United States, thereby facilitating data collection and exchange between these three regions.

For more information on MedDRA, interested readers are referred to http://www.meddramsso.com. More information on ICH can be found under http://www.ich.org.

Notice to applicants - a guideline on Summary of Product Characteristics

The PhVWP was informed that the European Commission has finalised and published the second revision of this guideline (see http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/smpc_guideline_rev2.pdf). The PhVWP had contributed to this revision with regard to presentation of safety information in the Summary of Product Characteristics (SmPCs). The SmPC describes the profile of a medicinal product in terms of quality, safety and efficacy and is part of the marketing authorisation of a medicine, setting out the authorised use of the product. Therefore, it is the basis of information for healthcare professionals on how to use a medicine safely and effectively.

International Conference on Pharmacoepidemiology

The PhVWP heard feedback from colleagues who participated in the International Conference on Pharmacoepidemiology (ICPE) in August 2009 and noted the latest developments in this field. Pharmacoepidemiology comprises the methods and activities for the investigation of effects of medicines in populations and is important for monitoring and assessing risks of medicinal products. The PhVWP agreed to prepare contributions during the first half of next year for ICPE 2010.

REGULATORY ABBREVIATIONS

CHMP – Committee of Medicinal Products for Human Use
CMD(h) – Co-ordination Group for Mutual Recognition and Decentralised Procedures for Human Medicines
EMEA – European Medicines Agency
EU – European Union
HMA – Heads of Medicines Agencies
PhVWP – CHMP Pharmacovigilance Working Party
PL – Package Leaflet
PASS – Post-Authorisation Safety Study
PSUR – Period Safety Update Report
RMP – Risk Management Plan
SmPC – Summary of Product Characteristics