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MONTHLY REPORT

PHARMACOVIGILANCE WORKING PARTY (PHVWP)

NOVEMBER 2009 PLENARY MEETING

The CHMP Pharmacovigilance Working Party (PhVWP) held its November 2009 plenary meeting on 16-18 November 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.

Cyproterone acetate - Risk of meningioma

Do not use cyproterone acetate in formulations containing 10mg or more in patients with meningioma or a history of meningioma.

Triggered by a publication in the medical literature (Froelich S, Dali-Youcef N, Boyer P, et al. Does cyproterone acetate promote multiple meningiomas? Endocrine Abstracts. 2008; 16: P158.), the PhVWP reviewed all available evidence on a possible causal relationship between cyproterone acetate (CPA) and the occurrence of meningioma. The review covered data from the medical literature, spontaneous reporting, a pharmacoepidemiological study, dose-responsiveness data as well as mechanistic considerations.

CPA exerts anti-androgenic properties upon the hormonal system. Formulations containing 10 to 300mg are used in severe hypersexuality or sexual deviation in men and in inoperable carcinoma of the prostate. Low dosage forms of 2mg and less are used to treat acne and hirsutism.

A meningioma is a generally benign tumour of the tissue layer between the brain and the skull.

In view of the available evidence, the PhVWP concluded that the administration of CPA at doses of 25mg and more for a long time period (i.e. years) could at least be possibly causally related with the occurrence of (multiple) meningiomas whereas there is substantially less evidence for such an association with dosage forms of 2mg or less.

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Therefore, the PhVWP recommended that the product information for formulations containing 10mg or more CPA should contain information on the possible risk of meningioma together with a contraindication in patients with meningioma or a history of meningioma.

For the formulations containing 2mg or less of CPA, an update to the product information was not considered necessary.

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 referred to the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

HMG-CoA reductase inhibitors (statins) - Risks of sleep disturbances, memory loss, sexual dysfunction, depression, interstitial lung disease and micturition disorders

Statins may cause sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease. Statins should be stopped if a patient develops interstitial lung disease.

The PhVWP conducted a review of the class of HMG-CoA reductase inhibitors[1], commonly called statins, triggered by spontaneously reported cases and information in the medical literature suggesting potential associations of statins with sleep disturbances, memory loss, sexual dysfunction, depression, interstitial lung disease and micturition disorders (problems with urination). Statins are widely-used medicines for patients with hypercholesterolaemia and dyslipidemia (raised cholesterol and lipids in the blood).

The PhVWP considered data from spontaneous reporting, clinical trials and the medical literature. The clinical trials provided evidence that for some statins the rates of sleep disturbances and memory loss were higher in the active than in the placebo group. Spontaneous case reports included cases with a temporal relationship, positive dechallenge and positive rechallenge, providing further supportive evidence of a possible causal relationship of sleep disturbances (e.g. sleeplessness, nightmares) and memory loss with statins. The spontaneous case reports also showed that statins may be associated with sexual dysfunction, depression and interstitial lung disease. The available evidence did not suggest that micturition disorders were associated with statins. The PhVWP recognised that the amount of evidence for the different adverse reactions varied among the statins but considered that there was no robust evidence to discriminate between the individual statins in terms of their risks.

The PhVWP concluded its review with the recommendation to update and harmonise the product information for statins across the EU to include sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease as possible adverse reactions and to advise to stop treatment with statins, should a patient develop interstitial lung disease.

The PhVWP informed the CMD(h) accordingly, and for the final wording 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 referred to the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

*Phenytoin and fosphenytoin - Risk of Stevens-Johnson syndrome in association with HLA-B*1502 allele*

*Oral phenytoin to be used in patients of Thai or Han Chinese ethnic origin known to be positive for HLA-B*1502 allele only if the benefits are considered to exceed risks due to increased risk of Stevens-Johnson syndrome.*

The PhVWP considered a recent publication in a medical journal showing a significant association between the gene allele HLA-B*1502 and phenytoin-induced Stevens-Johnson syndrome (SJS) in patients of Thai ethnic origin (Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin-induced Stevens-Johnson syndrome (SJS) is associated with HLA-B*1502 allele in Thai

[1] The review covered the following active substances: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin.

population. Epilepsia. 2008; 48:1015-1018). SJS is a serious side effect of the skin. The PhVWP also consulted the CHMP Pharmacogenomics Working Party on this safety concern.

As a result, the PhVWP recommended that the product information for the anti-epileptic phenytoin for oral administration should reflect that the HLA-B*1502 allele may be associated with an increased risk of developing Stevens-Johnson syndrome (SJS) in individuals of Thai or Han Chinese ethnic origin when treated with phenytoin and that oral phenytoin should only be used in such patients known to be positive for HLA-B*1502 if the benefits are considered to exceed the risks.

In the Caucasian and Japanese population, the frequency of the HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on any risk association. Adequate information about risk associations in other ethnicities is currently not available.

For phenytoin for intravenous administration and the pro-drug fosphenytoin, also for intravenous administration, the PhVWP considered that such intravenous administration occurs only in emergency care for one or two doses, and that therefore any risk is negligible. Thus, no changes to the product information for these products were recommended.

The PhVWP informed the CMD(h) accordingly, and for the final wording 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 referred to the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Propylthiouracil - Risk of serious liver injury

Stop propylthiouracil immediately if significant hepatic enzyme abnormalities develop. Serious hepatic disorders, including fatal cases, have been reported in adults and children during treatment with propylthiouracil.

Propylthiouracil (PTU) has been used for treatment of hyperthyroidism for more than 50 years. Following spontaneous reports of serious liver injury in both children and adults in the United States and the publication of an alert message by the US Food and Drug Administration (FDA) in June 2009, the PhVWP conducted a review of this safety concern.

After an analysis of all cases of serious liver injury identified from spontaneous reporting and the medical literature, the PhVWP recommended that the product information should be updated with information on the risk of serious liver injury in adults and children and the warning to stop PTU immediately if a patient develops significant hepatic enzyme abnormalities. In the reported cases, the time to onset varied, but in the majority of the cases, the liver reaction occurred within 6 months after starting the treatment.

The PhVWP will inform 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 referred to the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

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 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.

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