LONDON, 25 FEBRUARY 2010
EMA/102067/2010

ISSUE NUMBER: 1002

MONTHLY REPORT
PHARMACOVIGILANCE WORKING PARTY (PHVWP)
FEBRUARY 2010 PLENARY MEETING

The CHMP Pharmacovigilance Working Party (PhVWP) held its February 2010 plenary meeting on 15-17 February 2010.

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.ema.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.ema.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.

Fluoxetine – Risk of cardiovascular birth defects

Increased risk of cardiovascular birth defects associated with use of fluoxetine during the first three months of pregnancy

The PhVWP concluded upon recommendations for the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) for products containing fluoxetine with regard to the risk of

European Medicines Agency
7 Westferry Circus ● Canary Wharf
London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400
Facsimile +44 (0)20 7418 8668
E-mail info@ema.europa.eu
Website www.ema.europa.eu

HMA Management Group
Kevin O'Malley House
Earlsfort Centre ● Earlsfort Terrace
Dublin 2 ● Ireland
Telephone +353 1 63 43 453
E-mail hma-ps@imb.ie
Website http://www.hma.eu

cardiovascular birth defects associated with the use of fluoxetine during the first three months of pregnancy (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly, and for the final wordings to be included in the SmPCs and 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.

GUIDELINES AND GENERAL MATTERS

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

Pharmacovigilance for medicinal products used against novel Influenza A (H1N1) virus

Medicines used to treat or prevent influenza belong to the groups of antivirals and vaccines. The European Medicines Agency 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 Agency in this respect. In particular, the PhVWP contributes to the Agency's Pandemic Pharmacovigilance Rapid Response Expert Group (PREG) which provides advice on any emerging safety data on influenza vaccines. Updates on the activities undertaken and on product information of influenza medicines are reported to the public via the Agency's website http://www.ema.europa.eu/.

Appointment of three new Co-opted PhVWP Members

The PhVWP welcomed the appointment by CHMP of Dr Torbjørn Callreus, Dr Giampiero Mazzaglia and Dr Eugene van Puijenbroek as co-opted experts for the PhVWP in the area of pharmacoepidemiology and thanked the outgoing Co-opted PhVWP Members for their contributions. Since 2006 the PhVWP has benefited from the co-optation of eight PhVWP Members in various areas of expertise who supplement the competences of the 27 regular PhVWP Members appointed by Member States.

REGULATORY ABBREVIATIONS

CHMP – Committee of 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
PhVWP – CHMP Pharmacovigilance Working Party
PASS – Post-Authorisation Safety Study
PL – Package Leaflet
PSUR – Period Safety Update Report
RMP – Risk Management Plan
SmPC – Summary of Product Characteristics

ANNEX 1

SUMMARY ASSESSMENT REPORT OF THE PhVWP FEBRUARY 2010:

Fluoxetine – Risk of cardiovascular birth defects

Key message
Increased risk of cardiovascular birth defects associated with use of fluoxetine during the first three months of pregnancy

Safety concern and reason for current safety review
A study published in the literature [1] suggested a possible causal association between cardiovascular birth defects and the use of fluoxetine during the first three months of pregnancy.

Information on the data assessed
Following the review of the study by Diav-Citrin O et al [1] at the level of the PhVWP, the original marketing authorisation holder of fluoxetine was requested to conduct a systematic critical meta-analysis of all available epidemiological data regarding the effects of first trimester fluoxetine exposure and the risk of congenital malformations with a particular focus on cardiac defects. The meta-analysis included nine studies [1-9].

Outcome of the assessment
The PhVWP reviewed the results of the meta-analysis and concluded that the data suggested that the risk of having an infant with a cardiovascular defect following the use of fluoxetine during the first trimester is increased to approximately 2/100 compared with an expected rate of such birth defects of about 1/100 in the general population.

The PhVWP also considered that the small increase in risk of cardiovascular congenital malformations must be weighted against the risks of untreated depression during pregnancy.

Consequently, the PhVWP recommended that the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) for fluoxetine-containing products should be updated with regard to this increased risk of cardiovascular birth defects.

References
[1] Diav-Citrin O, Shechtman S, Weinbaum D, Wajnberg R, Avgil M, Di Gianantonio E, Clementi M, Weber-Schoendorfer C, Schaefer C, Ornoy A. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. Br J Clin Pharmacol. 2008; 66: 695-705.

[2] Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM; National Birth Defects Prevention Study. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med. 2007; 356: 2684-2692.

[3] Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. Can J Psychiatry. 2009; 54: 242-246.

[4] Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med. 1996; 335: 1010-1015.

[5] Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med. 2007; 356: 2675-2683.

[6] Källén BA, Otterblad Olausson P. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol. 2007; 79: 301-308.

[7] Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol. 2005; 106: 1289-1296.

[8] Oberlander TF, Grunau R, Mayes L, Riggs W, Rurak D, Papsdorf M, Misri S, Weinberg J. Hypothalamic-pituitary-adrenal (HPA) axis function in 3-month old infants with prenatal selective serotonin reuptake inhibitor (SSRI) antidepressant exposure. Early Hum Dev. 2008; 84: 689-697.

[9] Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihn S, Donnenfeld A, McCormack M, Leen-Mitchell M, Woodland C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA. 1993; 269: 2246-2248.