



25 March 2010
EMA/173011/2010
Patient Health Protection

Monthly Report

Pharmacovigilance Working Party (PhVWP)

March 2010 Plenary Meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its March 2010 plenary meeting on 15-17 March 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 <http://www.ema.europa.eu/htms/human/phv/reports.htm>). Any position agreed by the PhVWP for non-centrally authorised products forms a recommendation to Member States.

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

Antidepressants – Risk of bone fractures

Epidemiological studies show an increased risk of bone fractures in patients taking tricyclic antidepressants or selective serotonin re-uptake inhibitors; the mechanism remains unknown

The PhVWP concluded upon recommendations for the Summaries of Product Characteristics (SmPCs) and Package Leaflets (PLs) regarding the risk of bone fractures for both tricyclic antidepressants and selective serotonin re-uptake inhibitor antidepressants¹ (see Annex 1 for the Summary Assessment Report).

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

¹ The recommendations of the PhVWP apply to the following active substances: 1) tricyclic antidepressants: amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline; 2) selective serotonin re-uptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

and PLs as well as practical information on the implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

Isotretinoin for oral use – Risk of erythema multiforme

Patients should stop isotretinoin if a serious skin rash develops and see their physician

The PhVWP conducted a review of three types of severe skin reaction in relation to isotretinoin, a treatment authorised for severe acne.

For Stevens Johnson syndrome and toxic epidermal necrolysis, the PhVWP concluded that the currently available evidence does not support the addition of these skin conditions as adverse reactions to the product information. As a routine measure, new information which may arise on Stevens Johnson syndrome and toxic epidermal necrolysis will be reviewed within the assessment of the periodic safety update reports to be submitted regularly by the marketing authorisation holders.

For erythema multiforme (a serious type of skin rash), the PhVWP concluded on recommendations for the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) for isotretinoin-containing products for oral administration regarding this risk (see Annex 2 for the Summary Assessment Report).

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

Lamotrigine – No evidence of increased risk of fatal liver failure

Lamotrigine may cause liver failure but an increased risk of fatal outcome has not been confirmed

Following spontaneous reports of fatal liver failure, and because of a known causal relationship between lamotrigine and liver failure, the PhVWP conducted an in-depth review of all reported cases. The PhVWP concluded that there is no evidence for an increased risk of fatal liver failure causally related to lamotrigine. As a routine measure, any new information on liver disorders with fatal outcome will be kept under close monitoring (see Annex 3 for the Summary Assessment Report).

Omeprazole and esomeprazole – Risk of reduced plasma levels of clopidogrel due to interaction

Concomitant use of omeprazole or esomeprazole in patients taking clopidogrel discouraged

The PhVWP contributed to the CHMP review of the latest data on the effects of concomitant use of clopidogrel and proton-pump inhibitors (see Position Statement of 23 March 2010 on the Agency's website <http://www.ema.europa.eu/>). The PhVWP agreed to initiate the update of the product information for omeprazole or esomeprazole in accordance with the outcome of the review. The CMD(h) was informed accordingly, and the updates will be processed through the procedures for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures, as applicable.

PERFALGAN (paracetamol) 10 mg/ml solution for infusion – Risk of dosing errors in infants resulting in overdose with serious outcome

PERFALGAN (paracetamol) solution for infusion contains 10mg/ml; accidental overdosing of infants may have a serious outcome

PERFALGAN 10 mg/ml solution for infusion contains paracetamol and is indicated for the short-term treatment of moderate pain, especially following surgery, or fever in situations where intravenous administration is justified by an urgent therapeutic need or because other routes of administration are not possible.

The PhVWP noted that, as of 31 December 2009, 22 cases of paracetamol overdose had been reported worldwide in children aged 1 day to 1 year. The root-cause of this error lies in the confusion between milligrams (mg) and millilitres (ml), with children being given x ml when x mg had been prescribed, resulting in the administration of a dose 10 times higher than prescribed.

The PhVWP welcomed the fact that risk minimisation activities have been or will be initiated in Member States as appropriate. These activities may include a direct healthcare professional communication and a poster for paediatric wards in hospitals. These communication materials remind healthcare professionals of the following:

- the strength of the solution is 10 mg paracetamol per 1 ml;
- the dose recommendation is 7.5 mg/kg paracetamol per administration to full-term neonates, infants and children weighing less than 10 kg up to 4 administrations per day (i.e. 0.75 ml solution per kg x 4 times/d);
- small volumes are administered in paediatrics;
- there is need for extremely careful prescribing and administration of the product.

For children weighing less than 10 kg, the PhVWP concluded that amendments to the formulation/presentation of the product should be undertaken to minimise the risk of accidental overdose. Proposals from the marketing authorisation holder have been requested by the French competent authorities.

Serotonergic antidepressants – Risk of persistent pulmonary hypertension of the newborn

Women should tell their physician and midwife if they have been taking a serotonergic antidepressant during (late) pregnancy because of the risk of persistent pulmonary hypertension of the newborn

The PhVWP concluded on recommendations for the Summaries of Product Characteristics (SmPCs) and Package Leaflets (PLs) for products containing serotonergic antidepressants² with regard to the risk of persistent pulmonary hypertension of the newborn after exposure in-utero (see Annex 4 for the Summary Assessment Report).

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

² The review of the PhVWP covered the following active substances: citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine.

For information on the centrally authorised products containing duloxetine, readers are referred to the Agency's website (<http://www.ema.europa.eu/>).

YASMIN/YIRA (ethinylestradiol 30µg + drospirenone) – Risk of venous thromboembolism

New studies suggest that the risk of venous thromboembolism for YASMIN/YIRA contraceptives is between those of second and third generation pills

Venous thromboembolism (VTE) is a condition in which a blood clot (thrombus) forms in a venous blood vessel. If left untreated, the thrombus may limit blood flow in the leg or pelvis, causing deep vein thrombosis, or travel towards the lung, causing pulmonary embolism. One to two % of cases of pulmonary embolism are fatal.

VTE is a well-known but rare adverse reaction of oestrogen- and progestogen-containing contraceptives. Epidemiological studies have shown that the incidence of VTE in women with no known risk factors for VTE who use combined oral contraceptives (COCs) with a low dose (<50 µg) of ethinylestradiol (EE) combined with levonorgestrel ("second generation pills") is about 20 cases per 100,000 woman-years of COC use and about 40 cases per 100,000 women-years of COC use for products containing low-dose EE and desogestrel/gestodene ("third generation pills"). In women who do not take any hormonal contraception, 5 to 10 VTE cases occur per 100,000 woman-years. Around 60 VTE cases occur per 100,000 pregnancies.

Recently, two epidemiological studies were published³, both assessing the risk of VTE in current users of different types of COCs. The results of these studies confirmed what is currently known about this risk, but also suggested that the risk for the COCs YASMIN and YIRA might be higher than previously estimated, and between those of second and third generation pills. Products called YASMIN or YIRA contain 30µg of EE in combination with drospirenone.

The two studies were discussed by the PhVWP, and it was concluded that the new data should be reflected in the Summaries of Product Characteristics (SmPCs) for YASMIN and YIRA products. The amendment of the SmPCs will be processed via variations of the marketing authorisations within the mutual recognition procedure.

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.

CHMP Guideline on Duplicate Detection and Management of Individual Cases and Individual Case Safety Reports

The PhVWP was consulted on this guideline during its development led by the EudraVigilance Expert Working Group. Interested readers are referred to the Agency's website <http://www.ema.europa.eu/> for the upcoming public consultation.

³ Lidegaard Ø, Løkkegaard E, Svendsen A, Agger C. Hormonal contraception and risk of venous thromboembolism: a national follow-up study. Br Med J. 2009; 339: b2890.
van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestagen type: results of the MEGA case-control study. Br Med J. 2009; 339: b2921.

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 March 2010

Antidepressants – Risk of bone fractures

Key message

Epidemiological studies show an increased risk of bone fractures in patients taking tricyclic antidepressants or selective serotonin re-uptake inhibitors; the mechanism remains unknown.

Safety concern and reason for current safety review

A possible association of selective serotonin re-uptake inhibitor antidepressants (SSRIs) with bone fractures was discussed by the PhVWP in 2007 following the publication of a cohort study suggesting a 2-fold increased risk of clinical fragility fractures in adults of 50 years of age and older using SSRIs over a 5-year period and two further studies in which a causal association between SSRI use and reduced bone mineral density (BMD) was suggested. At that time it was noted that the signal appeared to be consistent across different studies and, therefore, the marketing authorisation holders were requested to further investigate this signal using data from clinical trials, spontaneous reporting and the scientific literature.

Based on these investigations and newly available literature on antidepressants, the PhVWP conducted their review of all available evidence for SSRIs as well as of tricyclic antidepressants (TCAs) [1-34].

Information on the data assessed

Results from animal studies were considered inconclusive with respect to the risk of bone fractures associated with SSRIs. In December 2007, the CHMP concluded that further animal studies in this respect were not justified.

From the pooled clinical trial data, the incidence of fractures among patients treated with paroxetine was increased compared to the placebo patient group.

Overall, the nine observational studies were of good quality, except for one which was merely descriptive and provided no usable risk estimates. All studies, however, had noteworthy limitations. The cohort studies were small in study population size and suffered from inaccurate exposure measurement, except for one which used longitudinal patient records from pharmacies. The case-control studies using administrative databases were larger, and the substantial number of exposed cases allowed the researchers to study the effects of dose and duration of current use. However, none of the studies was able to investigate the effects of dose and duration simultaneously. Unlike the cohort studies, the case-control studies were not or only partially able to adjust for potential confounding factors, because information on confounding factors is mostly not available in administrative databases. Three of the case-control studies performed sensitivity analyses, which showed that the results could not be fully explained by these unmeasured factors.

Only one study was able to distinguish data by individual substances. However, exposure and hence power was not sufficient for all substances to be studied in detail.

From the available data, no definite conclusion could be drawn regarding a dose-response relationship, time relationship or the underlying mechanism, which remains subject of debate.

Outcome of the assessment

Considering the available evidence and taking into account the limitations and strength of the evidence, the PhVWP recommended that a statement on the epidemiological findings of an increased risk of bone fractures with SSRIs and TCAs should be included in the product information for these products. The statement should also be explicit that the studies were mainly conducted in patients of 50 years of age and older and that the mechanism leading to this increased risk is unknown.

The recommendations of the PhVWP apply to the following active substances: 1) tricyclic antidepressants: amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline; 2) selective serotonin re-uptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

References

- [1] Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. *J Clin Psychopharmacol*. 2008; 28: 384-390.
- [2] Cauley JA, Fullman RL, Stone KL, Zmuda JM, Bauer DC, Barrett-Connor E, Ensrud K, Lau EMC, Orwoll ES. Factors associated with the lumbar spine and proximal femur bone mineral density in older men. *Osteoporos Int*. 2005; 16: 1525-1537.
- [3] Diem SJ, et al. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. *Arch Intern Med*. 2007; 167: 1240-1245.
- [4] Ensrud KE; Blackwell T; Mangione CM, Bowman PJ, Bauer DC, Schwartz A, Hanlon JT, Nevitt MC, Whooley MA. Central nervous system active medications and risk for fractures in older women. *Arch Intern Med*. 2003; 163: 949-957.
- [5] French DD, Campbell R, Spehar A, Cunningham F, Foulis P. Outpatient medications and hip fractures in the US: a national veterans study. *Drugs Aging*. 2005; 22: 877-885.
- [6] Haney EM, et al. Association of low bone mineral density with selective serotonin inhibitor used by older men. *Arch Intern Med*. 2007; 167: 1246-1251.
- [7] Haney EM, Warden SJ, Bliziotis MM. Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management?. *Bone*. 2009; Aug 5 2009 [Epub].
- [8] Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol Med Sci*. 2007; 62A(10): 1172-1181.
- [9] Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. *Am J Epidemiol*. 2003; 158: 77-84.
- [10] Kerse N, et al. Falls, depression, and antidepressants in later life: a large primary care appraisal. *Plos ONE*. 2008; 3(6): e2423.
- [11] Kimmel DB. Animal models for in vivo experimentation in osteoporosis research. In: Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis*. San Diego, CA: Academic Press; 1996: 671-690.
- [12] Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH. Bone mineral density in subjects using central nervous system-active medications. *Am J Med*. 2005; 118: 1414.

- [13] Landi F, et al. Psychotropic medications and risk for falls among community- dwelling frail older people: an observational study. *J Gerontol A Biol Sci Med Sci*. 2005; 60: 622-626.
- [14] Lapane KL, Gambassi G, Hume A, Sgadari A, Mor V. Which antidepressants increase the risk of femur fracture in long term care?. *J Am Geriatr Soc*. 1998; 46(S53):148.
- [15] Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet*. 1998; 351: 1303-1307.
- [16] Mezuk B, Eaton WW, Golden SH, Wand G, Lee HB. Depression, antidepressants, and bone mineral density in a population-based cohort. *J Gerontol A Biol Sci Med Sci*. 2008 ;63: 1410-1415.
- [17] Michelson D, Stratakis C, Hill L, et al. Bone mineral density in women with depression. *N Engl J Med*. 1996; 335: 1176-1181.
- [18] Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ 3rd. Psychotropic drug use and the risk of hip fracture. *N Engl J Med*. 1987; 316: 363-369.
- [19] Richards JB, et al (Canadian Multicentre Osteoporosis Study Research Group). Effect of selective serotonin reuptake inhibitors on the risk of fractures. *Arch Intern Med*. 2007; 167: 188-194.
- [20] Rosen CJ. Breaking into bone biology: serotonin's secrets. *Nature Medicine*. 2009;15: 145-146.
- [21] Schneeweiss S, Wang PS. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. *J Clin Psychopharmacol*. 2004; 24: 632-638.
- [22] Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, Melville JL, Lacroix AZ. Depressive symptoms, bone loss, and fractures in postmenopausal women. *J Gen Intern Med*. 2008; 23: 567-574.
- [23] Sterke CS, et al. The influence of drug use on fall incidents among nursing home residents: a systematic review. *International Psychogeriatrics*. 2008; 20: 890-910.
- [24] Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med*. 1998; 339: 875-882.
- [25] van den Brand MW, Pouwels S, Samson MM, van Staa TP, Thio B, Cooper C, Leufkens HG, Egberts AC, Verhaar HJ, de Vries F. Use of anti-depressants and the risk of fracture of the hip or femur. *Osteoporos Int*. 2009; Feb 24 2009 [Epub ahead of print].
- [26] Vestergaard P, Renjmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporosis Int*. 2006; 17: 807-816.
- [27] Vestergaard P, Rejnmark L, Mosekilde L. Selective serotonin reuptake inhibitors and other antidepressants and risk of fracture. *Calcif Tissue Int*. 2008; 82: 92-101.
- [28] Warden SJ, et al. Inhibition of the serotonin (5-hydroxytryptamine) transporter reduces bone accrual during growth. *Endocrinology*. 2005; 146: 685-693.
- [29] Warden SJ, Nelson IR, Fuchs RK, Bliziotis MM, Turner CH. Serotonin (5-hydroxytryptamine) transporter inhibition causes bone loss in adult mice independently of estrogen deficiency. *Menopause*. 2008; 15: 1176-1183.
- [30] Westbroek I, Waarsing JH, van Leeuwen JP, Waldum H, Reseland JE, Weinans H, Syversen U, Gustafsson BI. Long-term fluoxetine administration does not result in major changes in bone architecture and strength in growing rats. *J Cell Biochem*. 2007; 101:360-368.
- [31] Whooley MA, Kip KE, Cauley JA, et al. Depression, falls, and risk of fracture in older women. *Arch Intern Med*. 1999;159: 484-490.

[32] Williams LJ, et al. Selective serotonin reuptake inhibitor use and bone mineral density in women with a history of depression. *Int Clin Psychopharmacol*. 2008; 23: 84-87.

[33] Yadav YK, Ryu JH, Suda N, Tanaka KF, Gingrich JA, Schütz G, Glorieux FH, Chiang CY, Zajac JD, Insogna KL, Mann JJ, Hen R, Ducy P, Karsenty G. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell*. 2008; 135:825-837.

[34] Ziere G, Dielman JP, van der Cammen TJM, Hofman A, Pols HAP, Stricker BHCh. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of nonvertebral fractures. *J Clin Psychopharmacol*. 2008; 28: 411-417.

Annex 2

Summary Assessment Report of the PhVWP March 2010

Isotretinoin for oral use – Risk of erythema multiforme

Key message

Patients should stop isotretinoin if serious skin rash develops and see the physician.

Safety concern and reason for current safety review

This safety review was initiated by a marketing authorisation holder with the view of adding erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis to the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) of their product containing isotretinoin for oral administration.

The concerns arose from spontaneous case reports on these serious skin conditions and therefore the cases were assessed as to whether there was a possible causal association.

Information on the data assessed

A thorough assessment of all worldwide spontaneous case reports of erythema multiforme (44 cases), Stevens Johnson syndrome (15 cases) and toxic epidermal necrolysis (5 cases) and the scientific literature was undertaken at the level of the PhVWP.

In all cases of toxic epidermal necrolysis, the patients were receiving other medicines or had concurrent infections that are known to be associated with this serious skin condition. Given these alternative explanations as to why the individuals developed the skin condition, it was considered that a causal association could not be established.

For Stevens Johnsons syndrome, in many cases there were likewise alternative explanations for the occurrence of this skin condition or the information in the case reports was too limited, and therefore a causal association could not be established.

Erythema multiforme was the most commonly reported of these serious skin conditions. In more than half of the cases (26 cases) there were no alternative explanations for the occurrence of this skin condition. In some cases (7), there was clear evidence that the patient recovered from the condition after isotretinoin was stopped, and in some other cases (4) there was evidence that the erythema multiforme rash reoccurred when isotretinoin was reintroduced. Overall, the cases of erythema multiforme were considered to provide sufficient evidence to suggest a causal association with isotretinoin.

Erythema multiforme is a serious form of skin rash, appearing initially as circular patches, often with a central blister, usually on arms and hands or legs and feet but can affect any part of the body.

Outcome of the assessment

Based on the available data, the PhVWP concluded with the recommendation that the risk of erythema multiforme should be added to the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) of products containing isotretinoin for oral use as an adverse reaction, with advice to patients to stop isotretinoin if serious skin rash develops and to see the physician.

For Stevens Johnson syndrome and toxic epidermal necrolysis, the PhVWP concluded that the currently available evidence did not support the addition of these skin conditions as adverse reactions to the product information. As a routine measure, new information which may arise on Stevens Johnson syndrome and toxic epidermal necrolysis will be reviewed within the assessment of the periodic safety update reports to be submitted regularly by the marketing authorisation holders.

Annex 3

Summary Assessment Report of the PhVWP March 2010

Lamotrigine – No evidence of increased risk of fatal liver failure

Key message

Lamotrigine may cause liver failure but an increased risk of fatal outcome has not been confirmed.

Safety concern and reason for current safety review

Cases of fatal liver failure in association with lamotrigine were reported spontaneously; some of them were published in the scientific literature. This raised concern, in particular relating to young women.

Lamotrigine is known to be causally related with elevated liver enzyme levels, liver dysfunction and liver failure, and doses should be reduced in patients with hepatic impairment. This is already reflected in the product information.

Given the fatal outcome of the case reports, a review of the new concern was requested from the original marketing authorisation holder.

Information on the data assessed

12 cases of fatal liver failure had been reported, out of which 6 concerned women in the age range of 15 to 35 years. In this age range, there was no report for male patients. At least 3 out of the 6 young females experienced adverse events suggestive of a hypersensitivity syndrome resulting in fatal liver failure.

In some patients, the concomitant use of valproic acid may have caused or contributed to the fatal liver failure. Valproic acid is known to cause hepato-biliary disorders with fatal outcome and the inhibition of glucuronidation of lamotrigine by valproic acid is mentioned in the product information for lamotrigine.

In 6 cases (4 female, 2 male), there was concomitant use of paracetamol which is known to cause fatal liver failure in overdose. In 1 case out of the 6, paracetamol was indicated as the suspected medicine to have caused the fatal liver failure.

Other risk factors for fatal liver failure were reviewed for each case.

Outcome of the assessment

After this in-depth review of all reported cases, the PhVWP concluded that there is no evidence for an increased risk of fatal liver failure causally related to lamotrigine. There were 6 cases of fatal liver failure reported with concomitant use of lamotrigine and paracetamol, and excluding the cases with alternative risk factors, there seems to be only 1 case concerning a possible causal relationship with concomitant use of lamotrigine and paracetamol. This single case does not provide evidence

warranting amendments to the product information with regard to a possible interaction between these two active substances. As a routine measure, any new information on liver disorders with fatal outcome will be kept under close monitoring.

Annex 4

Summary Assessment Report of the PhVWP March 2010

Serotonergic antidepressants – Risk of persistent pulmonary hypertension of the newborn

Key message

Women should tell their physician and midwife if they have been taking a serotonergic antidepressant during (late) pregnancy because of the risk of persistent pulmonary hypertension of the newborn.

Safety concern and reason for current safety review

The PhVWP considered new studies published in the scientific literature with regard to a possible risk for persistent pulmonary hypertension of the newborn (PPHN) when the mother has taken a serotonergic antidepressant during pregnancy.

PPHN is a condition where a newborn's blood circulation system does not adapt to breathing outside the womb due to high blood pressure in the lungs. In this condition, the blood flow in the lungs and heart is abnormal and the newborn cannot get enough oxygen into the blood, making the baby breathe faster and appear bluish. These symptoms of PPHN usually begin within 24 hours after birth. In the general population, 1 to 2 cases of PPHN occur per 1000 births.

The review of the PhVWP covered the following active substances: citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine.

Information on the data assessed

Since the last review of this safety concern in 2006/07, three new studies have been published in the scientific literature [1-3].

An epidemiological study [1] used data from the Swedish Medical Birth Register from 1997 to 2005 to evaluate an association between the use of selective serotonin re-uptake inhibitors (SSRIs) during pregnancy and PPHN and supported the results from a previously published study [4], which had shown an association between the use of SSRIs during pregnancy and PPHN. The new study [1] was considered to provide stronger evidence because the exposure information was collected prospectively, while the previous study [4] was based on retrospective collection of data on medicines used during pregnancy.

Another study [2] sought to determine the prevalence of PPHN among infants whose mothers were exposed to antidepressants in the third trimester of pregnancy and found no association between SSRIs and PPHN. The study was considered to have several limitations, including incomplete detection of PPHN cases and the small overall number (5) of identified cases. This means that the study did not have sufficient power to detect an association, if any, of PPHN and exposure to SSRIs in late pregnancy. Other limitations of the study refer to missing information on potential confounding factors such as maternal body mass index, smoking, exposure to alcohol and substance abuse.

A further study [3] evaluated the effect of fluoxetine on rat pulmonary and vascular smooth muscle mechanical properties and on cell proliferation. The study concluded that in-utero exposure to fluoxetine induces pulmonary hypertension in the foetal rat, as a result of an increase in pulmonary vascular smooth muscle proliferation.

Outcome of the assessment

The PhVWP concluded their review with recommendations to update the product information of serotonergic antidepressants. While the available evidence refers to SSRIs, the PhVWP concluded that the product information for other serotonergic antidepressants (duloxetine, mirtazapine, venlafaxine) should also be updated, though specifying that the evidence was gained from SSRIs. This conclusion took into account the similar mechanism of action of these three substances.

The updated product information should make patients and healthcare professionals aware of the risk of PPHN and encourage women to report to their physician and midwife if they have been taking a serotonergic antidepressant during pregnancy, particularly in late pregnancy. It should also urge parents to contact the physician or midwife immediately if symptoms of PPHN occur.

In quantitative terms, the risk of PPHN after in-utero exposure to serotonergic antidepressants was considered very low (approximately 5 cases per 1000 births).

References

- [1] Kallen B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Safety*. 2008 ; 17:801-806.
- [2] Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Safety*. 2009; 18: 246-252.
- [3] Fornaro E, Pan J, Belik J. Prenatal exposure to fluoxetine induces fetal pulmonary hypertension in the rat. *Am J Respir Crit Care Med*. 2007; 176: 1035-1040.
- [4] Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *New Engl J Med*. 2006; 354:579-587.