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PhVWP Monthly report on safety concerns, guidelines and general matters

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The CHMP Pharmacovigilance Working Party (PhVWP) held its March 2012 plenary meeting on 12-14 March 2012.

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 meeting highlights from the CHMP published under http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=.

PERFALGAN (paracetamol) 10 mg/ml solution for infusion – Risk of medication errors resulting in overdose

PERFALGAN (paracetamol) solution for infusion contains 10 mg/ml; accidental overdosing of neonates and infants (due to medication errors following confusion between mg and ml) and underweight adults may have serious outcomes. In order to minimise this risk, the prescribed dose to be administered should always be specified as volume in ml, and careful adherence to weight-based dosing recommendations is necessary in all patients (both children and adults) weighing ≤ 50 kg.

The PhVWP conducted a review, in follow-up to their review of March 2010, of cases of accidental overdose occurring with the paracetamol-containing product PERFALGAN 10 mg/ml solution for

infusion. The PhVWP agreed upon updated risk minimisation measures and recommended rapid communication to healthcare professionals (see Annex 1 for the Summary Assessment Report).

Proton-pump inhibitors – Risk of bone fracture

Use of proton-pump inhibitors (PPIs), especially if used in high doses and over prolonged periods (> 1 year), may modestly increase the risks of hip, wrist and spine fracture, predominantly in the elderly or in those with other recognised risk factors. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.

Following the publication of several pharmacoepidemiological studies, the PhVWP reviewed data from clinical trials and observational studies investigating the risk of fracture with use of proton-pump inhibitors (PPIs)¹. The PhVWP concluded that the modestly increased risk of fracture observed with PPIs should be included in the product information for the respective medicinal products authorised in the EU for use on prescription-only (see Annex 2 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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.

SSRIs – Update of product information to reflect animal data on the effect on sperm quality and an evaluation of its human relevance

The product information for selective serotonin receptor inhibitors (SSRIs) in the EU should be updated to reflect that results of animal studies suggest that SSRIs may affect sperm quality but that no impact on male fertility in humans has been observed. Patients should not stop taking SSRIs on the basis of these findings. Patients with concerns should contact their physician.

Following information from published studies, the PhVWP reviewed the effects of selective serotonin receptor inhibitors (SSRIs)² on sperm quality and considered whether there is evidence for an impact on male fertility. The PhVWP concluded their review with recommendations for updating the product information of the respective medicinal products authorised in the EU (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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.

Lovastatin – Risk of new onset diabetes

The PhVWP agreed a revision of their review outcome of December 2011 on HMG-CoA reductase inhibitors and risk of new onset diabetes, clarifying that lovastatin had been included in the review and that the product information of all lovastatin-containing medicinal products in the EU should be amended accordingly. The PhVWP Monthly Report December 2011 (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500120115.pdf) was

¹ The active substances included in this review were esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

² The active substances included in this review were citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

revised accordingly, and the PhVWP informed the CMDh. For the final wording to be included in the product information, i.e. 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.

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMDh – Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

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 March 2012

PERFALGAN (paracetamol) 10 mg/ml solution for infusion – Risk of medication errors resulting in overdose

Key message

PERFALGAN (paracetamol) solution for infusion contains 10 mg/ml; accidental overdosing of neonates and infants (due to medication errors following confusion between mg and ml) and underweight adults may have serious outcomes. In order to minimise this risk, the prescribed dose to be administered should always be specified as volume in ml, and careful adherence to weight-based dosing recommendations is necessary in all patients (both children and adults) weighing ≤ 50 kg.

Safety concern and reason for current safety review

Cases of accidental overdose in children were reported for the paracetamol-containing product PERFALGAN 10 mg/ml solution for infusion. The root-cause of this dosing 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, in March 2010, noted this risk and risk minimisation measures in Member States. At that time, the PhVWP concluded that for children weighing ≤ 10 kg amendments to the formulation/presentation of the product should be undertaken to minimise the risk of accidental overdose and noted that proposals from the marketing authorisation holder had already been requested by the French competent authorities (see PhVWP Monthly Report March 2010).

In the meantime, cases of accidental overdose were also reported in underweight adults.

The PhVWP undertook a comprehensive follow-up review of the risk of medication errors with PERFALGAN 10 mg/ml.

Clinical setting

The medicinal product 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.

Information on the data assessed

The follow-up review was based on the periodic safety update reports, which have to be submitted regularly by the marketing authorisation holder. The marketing authorisation holder was also requested to provide an updated risk minimisation plan with risk minimisation measures to prevent these medication errors. The marketing authorisation holder also submitted proposals for a new presentation of the medicinal product for neonates and infants.

Outcome of the assessment

The PhVWP concluded this review with recommending new risk minimisation measures with two distinct components: Firstly, a number of measures were agreed to avoid unintentional overdose in

neonates and infants due to confusion between ml and mg. This follows continuing reports of accidental overdose with PERFALGAN 10 mg/ml solution for infusion in neonates and infants. Secondly, a general requirement for weight-based dosing was recommended to be added to the product information and to be reinforced via a direct healthcare professional communication. This follows reports of harm due to accidental overdosing in underweight adults (who had additional hepatic risk factors).

The PhVWP agreed upon an updated risk minimisation plan and recommended rapid communication to healthcare professionals and the production of new educational materials. The communication should include a dosing chart for children weighing ≤ 10 kg and the following clear statements:

- the strength of the solution is 10 mg paracetamol per 1 ml;
- the maximum dose is 7.5 mg/kg paracetamol per administration to full-term neonates, infants and children weighing ≤ 10 kg up to 4 administrations per day (i.e. 0.75 ml solution per kg x 4 times/d);
- the dose to be administered should always be specified as volume in ml;
- small volumes are administered in paediatrics; the volume of a single administration for children weighing ≤ 10 kg should never exceed 7.5 ml and will be less in lighter children;
- dosing for all patients weighing ≤ 50 kg should be careful and weight-based.

The PhVWP noted that the marketing authorisation holder's proposals for a new presentation of the medicinal product for neonates and infants are currently under review by the French competent authorities.

Annex 2

Summary Assessment Report of the PhVWP March 2012

Proton-pump inhibitors – Risk of bone fracture

Key message

Use of proton-pump inhibitors (PPIs), especially if used in high doses and over prolonged periods (> 1 year), may modestly increase the risks of hip, wrist and spine fracture, predominantly in the elderly or in those with other recognised risk factors. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.

Safety concern and reason for current safety review

A PhVWP review of data from clinical trials and observational studies was prompted by the publication of several pharmacoepidemiological studies [1-10] investigating the risk of fracture with use of proton-pump inhibitors (PPIs).

The evidence from pharmacoepidemiological studies [1-10] and meta-analyses of these studies [11, 12] suggested that there is a modest increase in fracture overall (by 10-40%), and specifically hip fracture (by 10-50%) and spine fracture (by 30-80%)³. The risk increased for those patients on PPIs long-term (> 1 year) and treated at higher doses.

Clinical setting

Proton-pump inhibitors (PPIs) are indicated for treatment of duodenal and gastric ulcers and are used in combination with antibacterials for the eradication of *Helicobacter pylori*. They are also used to treat gastroesophageal reflux disease, dyspepsia and Zollinger-Ellison syndrome. Further, PPIs are used for prevention and treatment of NSAID-associated ulcers.

The active substances included in this review were esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

Information on the data assessed

Originator marketing authorisation holders were contacted to provide a review of evidence from long-term clinical trials and to discuss the pharmacoepidemiological evidence and potential pathophysiological mechanism.

Outcome of the assessment

The PhVWP considered that several potential pathophysiological mechanisms could have a role in increasing the risk of bone fractures with PPIs. Potential mechanisms discussed by marketing authorisation holders on the basis of evidence from published literature were effects on calcium balance, magnesium balance, vitamin D and parathyroid hormone levels, and inhibition of vacuolar

³ Meta-analysis by Kwok et al (2010) [11] found:
OR=1.20 (95% CI 1.11-1.30) for any fracture;
OR=1.23 (95% CI 1.11-1.36) for hip fracture;
OR=1.50 (95% CI 1.32-1.72) for spine fracture.

Meta-analysis by Eom et al (2011) [12] found:
OR=1.29 (95% CI 1.18-1.41) for any fracture;
OR=1.31 (95% CI 1.11-1.54) for hip fracture;
OR=1.56 (95% CI 1.31-1.85) for spine fracture.

H⁺-ATPase and its effects on bone turnover. However, there is currently no unequivocal pharmacological explanation for the increased risk of fracture.

No robust evidence to support the signal raised by the pharmacoepidemiological studies was available from long-term clinical trials (> 1 year) provided by marketing authorisation holders. However, these trials were not designed with the outcome of fractures or bone disorders in mind and the population may not have included those most at risk of fracture.

The majority, but not all of the pharmacoepidemiological studies reported a modest increase in the risk of fractures of the hip, wrist or spine [1-10]. There were inconsistencies between studies in terms of the magnitude of the risk and the duration of time-to-event. PPIs increased the risk of hip fracture significantly after exposure of at least 1 year, 2 years and 7 years respectively in three studies [1, 8, 3]. Two meta-analyses [11, 12] of the published pharmacoepidemiological studies reported adjusted odds ratios of 1.20 (95% CI 1.11–1.30) and 1.29 (95% CI 1.18–1.41) for any fracture, 1.23 (95% CI 1.11–1.36) and 1.31 (95% CI 1.11–1.54) for hip fracture, 1.50 (95% CI 1.32–1.72) and 1.56 (95% CI 1.31–1.85) for spine fracture. The size of estimated risk increased with increased dose and duration of use.

The primary studies [1-10] varied with respect to the potential confounders that were adjusted for. Age, sex and concomitant medication were amongst the variables included in the adjustments. Some studies lacked information on important potential confounders such as smoking, alcohol abuse, body mass index and calcium and vitamin D exposure. One study [4], which excluded subjects with potential risk factors for fractures, did not find an association between PPI use and increased risk of fracture. Use of PPIs obtained over-the-counter without prescription was not examined in these studies.

Two pharmacoepidemiological studies that estimated attributable risk in two different cohorts reported that 3.6% of non-spine fractures [5] and 1.78% of hip fractures [8] could be attributed to the use of PPIs. The frequency of fractures in association with PPIs was estimated as 'uncommon' on the basis of the crude incidence rates reported in one study which matched two groups by birth year, sex, health plan enrolment date and membership duration in the Kaiser Permanente of Northern California healthcare system [8]. For those not exposed to PPIs, the incidence of hip fractures was 2.14 per 1000 person-years. For those with at least a 365 day supply of PPIs, the fracture incidence after this exposure period was increased to 3.24 per 1000 person-years. The authors reported that these estimates are within the range of prior population-based reports of fracture incidence.

Based on these data, the PhVWP recommended that the modestly increased risk of fracture observed with PPIs should be included in the product information for all medicinal products authorised in the EU containing esomeprazole, lansoprazole, omeprazole, pantoprazole or rabeprazole for use upon prescription-only. The evidence was not considered sufficiently robust to indicate an increase in risk for PPI-containing medicinal products available without prescription, as these are only authorised for short-term use.

For the summaries of product characteristics, the PhVWP recommended that

- the section 4.4 on warnings and precautions for use includes the following information: PPIs, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture by 10 to 40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium; and
- the section 4.8 on undesirable effects includes fractures of the hip, wrist or spine as adverse reactions with the frequency category 'uncommon'.

For the package leaflets, the PhVWP recommended to include the information that taking a PPI, especially over a period of more than 1 year, may slightly increase the risk of fractures in the hip, wrist or spine, followed by the advice to patients to inform the physician if s/he has osteoporosis or is taking corticosteroids.

References

- [1] Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *J Am Med Assoc.* 2006; 296: 2947-2953.
- [2] Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int.* 2006; 79: 76-83.
- [3] Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *Can Med Assoc J.* 2008; 179: 319-326.
- [4] Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. *Pharmacotherapy.* 2008; 28: 951-959.
- [5] Yu EW, Blackwell T, Ensrud KE, Hillier TA, Lane NE, Orwoll E, Bauer DC. Acid-suppressive medications and risk of bone loss and fracture in older adults. *Calcif Tissue Int.* 2008; 83: 251-259.
- [6] de Vries F, Cooper AL, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving acid-suppressant medication alone and in combination with bisphosphonates. *Osteoporos Int.* 2009; 20:1989-1998.
- [7] Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, Chen Z. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med.* 2010; 170: 765-771.
- [8] Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology.* 2010; 139: 93-101.
- [9] Lalmohamed A, Pouwels S, Cooper C, van Staa TP, Leufkens B, de Boer A, de Vries F. Use of proton pump inhibitors and risk of hip fracture. *Bone.* 2009; 44(Suppl2): S396-S397.
- [10] Roux C, Briot K, Gossec L, Kolta S, Blenk T, Felsenberg D, Reid DM, Eastell R, Glüer CC. Increase in vertebral fracture risk in postmenopausal women using omeprazole. *Calcif Tissue Int.* 2009; 84: 13-19.
- [11] Kwok CS, Yeong JK, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. *Bone.* 2011; 48: 768-776.
- [12] Eom CS, Park SM, Myung SK, Yun JM, Ahn JS. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. *Ann Fam Med.* 2011; 9: 257-267.

Annex 3

Summary Assessment Report of the PhVWP March 2012

SSRIs – Update of product information to reflect animal data on the effect on sperm quality and an evaluation of its human relevance

Key message

The product information for selective serotonin receptor inhibitors (SSRIs) in the EU should be updated to reflect that results of animal studies suggest that SSRIs may affect sperm quality but that no impact on male fertility in humans has been observed. Patients should not stop taking SSRIs on the basis of these findings. Patients with concerns should contact their physician.

Safety concern and reason for current safety review

Following information from some published studies, a review of the effect of paroxetine on sperm quality and the evidence for any possible impact on male fertility had previously been conducted, using the medical literature, clinical studies and the originator marketing authorisation holder's clinical safety database.

In March 2010, the product information for paroxetine had been updated to reflect the information available at that time for this active substance. The medical literature reviewed within the variation procedure for paroxetine [e.g. 1, 2] had been insufficient to conclude on a class-effect for the other selective serotonin receptor inhibitors (SSRIs) used in depression, obsessive compulsive disorder and anxiety disorders. This was due to varying observations across different SSRIs in the relevant publications.

The PhVWP therefore agreed to perform an updated review of all available data concerning this issue in order to determine whether this could be a class-effect.

Information on the data assessed

Originator marketing authorisation holders for citalopram, escitalopram, fluoxetine, fluvoxamine and sertraline were contacted to provide all available data from clinical trials, non-clinical (animal) studies, observational studies and spontaneous reporting as well as their data reviews on effects on sperm quality (i.e. the ability of the sperm to accomplish fertilisation) and impact on male fertility. For paroxetine, these data had been requested and assessed previously.

Outcome of the assessment

The data showed impairment of sperm quality and findings regarding male fertility in animals with all SSRIs, except for sertraline, as follows:

- For fluvoxamine, adverse effects were observed with plasma levels of the active substance three times higher than those achieved in humans in clinical use, which does not completely exclude clinical relevance, as individual variability may occur. Clinical data for fluvoxamine were not available with regard to impact on human fertility.

- For citalopram, effects were observed with plasma levels of the active substance in excess of those achieved in humans in clinical use. Clinical data do not confirm effects for citalopram in humans, and were not available for escitalopram.
- For fluoxetine, animal studies suggested that there might be an effect on sperm quality, but an effect on male fertility was only seen in doses higher than the maximum tolerable dose. These findings were not confirmed by clinical data for humans.

The PhVWP considered that although there were differences in the animal data, overall these animal studies showed that SSRIs may affect sperm quality. In animal models, most SSRIs were associated with effects on male fertility at plasma levels above those achieved in humans in clinical use. There were a small number of patient case reports that described an effect of SSRIs on sperm quality. In these rare cases, the effects were reversible. No studies specifically investigating effects on male fertility in humans had been performed, but in the available clinical data no impaired male fertility in humans in association with SSRIs was observed.

The PhVWP concluded their review, recommending that the above information on the effect of SSRIs on sperm quality and male fertility should be included in the product information of all medicinal products authorised in the EU which contain citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline. Therefore section 5.3 of the summaries of product characteristics on pre-clinical safety data and section 4.6 on fertility should be updated with the data available for each active substance respectively and with the statements that observed effects, if any, on sperm quality in humans were reversible and that impaired male fertility in humans has so far not been observed. The package leaflets should be updated accordingly.

Patients should not stop taking SSRIs on the basis of these findings. Patients with concerns should contact their physician.

References

- [1] Tanrikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. *Urology*. 2007; 69: 185.e5-7.
- [2] Safarinejad MR. Sperm DNA damage and semen quality impairment after treatment with selective serotonin reuptake inhibitors detected using semen analysis and sperm chromatin structure assay. *J Urol*. 2008; 180: 2124-2128.