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

The CHMP Pharmacovigilance Working Party (PhVWP) held its January 2010 plenary meeting on 18-20 January 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.

Hormone Replacement Therapy containing oestrogen with and without progesterone – 3rd revision of Core Summary of Product Characteristics

Product information of HRT products updated on risks of breast cancer, ovarian cancer, endometrial cancer, coronary artery disease, stroke and venous thrombosis

A Core Summary of Product Characteristics (Core SmPC) for Hormone Replacement Therapy (HRT) products containing oestrogen with and without progesterone has, since 2001, been regularly

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

updated at the level of the EU by the CMD(h) (previously by the Mutual Recognition Facilitation Group). The contribution of the PhVWP to the third revision of the Core SmPC was on the risks of HRT in relation to breast cancer, ovarian cancer, endometrial cancer, coronary artery disease, stroke and venous thrombosis (see Annex 1 for the Summary Assessment Report). Interested readers may visit the HMA website (http://www.hma.eu/cmdh.html) for the latest updated Core SmPC. The Core SmPC will serve as the basis for updating product information for all HRT products authorised in the Member States of the EU for the treatment of post-menopausal women.

Salmon calcitonin – No association with progression of prostate cancer

Available data do not provide evidence for causal association between salmon calcitonin and progression of prostate cancer

The PhVWP considered that current evidence in relation to salmon calcitonin and a possible risk of progression of prostate cancer remains limited and concluded that no amendment to the Summary of Product Characteristics or other regulatory action was warranted. Monitoring of this issue will however continue (see Annex 2 for the Summary Assessment Report).

Salmon calcitonin, in its injectable formulation, is authorised for the prevention of acute bone loss due to sudden immobilisation (e.g. in patients with recent osteoporotic bone fractures), Paget's disease of the bone and hypercalcaemia of malignancy.

Valproic acid – Interaction with carbapenems

Avoid concomitant use of carbapenems and valproic acid/sodium valproate because of reduced valproate plasma concentrations

The PhVWP concluded upon recommendations for the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) for products containing the antiepileptics valproic acid or sodium valproate with regard to the interactions with carbapenem antibiotics (see Annex 3 for the Summary Assessment Report). The interaction has been reported to result in a 60-100% decrease in valproate plasma concentrations within about two days.

The PhVWP informed the CMD(h) accordingly. 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

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

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/.

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 JANUARY 2010:

Hormone Replacement Therapy containing oestrogen with and without progesterone – 3rd revision of Core Summary of Product Characteristics

Key message
Product information of HRT products updated on risks of breast cancer, ovarian cancer, endometrial cancer, coronary artery disease, stroke and venous thrombosis

Reason for current safety review
A Core Summary of Product Characteristics (Core SmPC) for Hormone Replacement Therapy (HRT) products containing oestrogen with and without progesterone has been regularly updated at the level of the EU by the CMD(h) (previously by the Mutual Recognition Facilitation Group) since 2001. The third revision of the Core SmPC was initiated to provide accurate information on the latest evidence.

Safety concern and data assessed
Latest evidence was mainly available from the Women's Health Initiative (WHI) trial (additional results for heart disease, stroke, venous thromboembolism and breast cancer) and the Million Women Study (MWS) (new findings on ovarian cancer and updated findings on breast cancer). There were also important meta-analyses of coronary heart disease and breast cancer and new observational data on stroke as well as endometrial and ovarian cancer.

Outcome of the assessment
The third revision of the core SmPC includes a new contra-indication (known thrombophilic disorders), new or adapted warnings regarding premature menopause, endometrial cancer risk of oestrogen-only HRT, breast cancer risk, ovarian cancer risk, venous thromboembolism risk, coronary artery disease risk and adapted wordings on undesirable effects (breast cancer, endometrial cancer, venous thromboembolism and stroke).

More specifically, it provides advice that the risks of HRT are likely to outweigh the benefits for the majority of women above the age of 60 years and that the risk is lower in women taking HRT during premature menopause. Further it includes the clearer evidence that the risk profile in women without a uterus using oestrogen-only HRT is more favourable than that associated with combined HRT.

The following was concluded in relation to particular risks:

- Breast cancer: There is uncertainty over the increase in incidence of breast cancer in oestrogen-only users, given that low or no risk was observed in many recent studies including WHI. There is new evidence from the WHI trial on risks associated with oestrogen-only HRT, including lack of increase in risk of breast cancer in users of oestrogen-only compared with combined HRT.

- Endometrial cancer: In MWS, no risk was observed in users of combined sequential or continuous HRT.

- Ovarian cancer: There is possibly a small increase in risk in users of combined HRT. Estimates on additional numbers of cases in users of any HRT are available from MWS.

- Coronary artery disease: An increase in risk is likely to be found only in combined HRT users, not in oestrogen-only HRT users. The risk increases with age. There is new evidence from the WHI trial on risks associated with oestrogen-only HRT, including lack of increase in risk of coronary artery disease in users of oestrogen-only compared with combined HRT.

- Stroke: Data from the WHI trial show the same increase in risk of stroke in users of oestrogen-only HRT as in users of combined HRT, which is independent of duration of use.

- Venous thromboembolism: A contra-indication of known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency) has been warranted necessary. There is new evidence

from the WHI trial on risks associated with oestrogen-only HRT, including a lower risk of VTE compared with combined HRT.

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ANNEX 2

SUMMARY ASSESSMENT REPORT OF THE PhVWP JANUARY 2010:

Salmon calcitonin – Association of progression of prostate cancer

Key message
Available data do not provide evidence for causal association between salmon calcitonin and progression of prostate cancer

Reason for current safety review
Recently published studies suggested that calcitonin may be associated with prostate cancer progression.

Clinical setting
Salmon calcitonin, in its injectable formulation, is authorised for the prevention of acute bone loss due to sudden immobilisation (e.g. in patients with recent osteoporotic bone fractures), Paget's disease of the bone and hypercalcaemia of malignancy.

Safety concern and data assessed
A review of the available evidence for salmon calcitonin and the suspected causal association with prostate cancer progression was discussed in July 2009 and additional data were reviewed by the PhVWP in January 2010 [1-3].

These reviews included all available data from pre-clinical, clinical studies and spontaneous reporting as well as a number of published studies [1, 4-13].

The main body of evidence suggesting a possible causal association between calcitonin and prostate cancer progression is limited to in vitro studies and artificial animal models. Extrapolation of this data to clinical practice is not possible.

Outcome of the assessment
The suspected causal association between prostate cancer progression and calcitonin has been primarily supported by published studies both in vitro and in vivo. The physiological significance however of these observations is not clear. All studies were conducted with human and not salmon calcitonin, at doses significantly higher than the ones used in clinical practice. Furthermore, these results were not confirmed in the simple and more physiologically relevant pre-clinical studies conducted in mice and rats.

Finally, there is no evidence from the clinical studies conducted for the salmon calcitonin-containing product MIACALCIC® and the spontaneous reporting to suggest a possible causal link between prostate cancer progression and calcitonin. Studies published in the literature with human data are very limited and do not support a causal association between calcitonin and prostate cancer progression.

Therefore regulatory action to address this issue was not considered to be justified at this time. However, it has been agreed that the next periodic safety update report for MIACALCIC® to be submitted by the marketing authorisation holder should include a focused assessment on tumour progression when used in cancer patients.

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ANNEX 3

SUMMARY ASSESSMENT REPORT OF THE PhVWP JANUARY 2010:

Valproic acid – Interaction with carbapenems

Key message
Avoid concomitant use of carbapenems and valproic acid/sodium valproate because of reduced valproate plasma concentrations.

Reason for current safety review
Recently, the product information for antibiotics of the carbapenem class was updated with information on the interaction with the antiepileptic valproic acid.

Safety concern and data assessed
The interaction between carbapenems and valproic acid has been well established, based on a number of case reports and at least one study [1] describing a clinically relevant interaction (electroclinical deterioration). The interaction has been reported to result in a 60-100% decrease in valproate plasma concentrations within about two days. The underlying mechanism has still to be elucidated, and several possible mechanisms have been proposed in the literature [2]. A further unpublished interaction study in healthy human volunteers demonstrated a large interaction between doripenem and valproic acid; during concomitant administration, the valproate plasma levels declined fast and significantly. Decreased plasma levels means that the therapeutic effect of valproic acid may be reduced.

Monitoring of valproate plasma levels or dose adjustments were considered as unlikely to manage the interaction, given its large magnitude and its time course which has not been fully characterised.

Therefore, the CHMP[1] and the PhVWP recently concluded that the concomitant use of carbapenems and valproic acid/sodium valproate is not recommended and that the Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) for carbapenems should be updated accordingly.

The SmPC and PL for valproic acid presently contain very limited information on this interaction.

Outcome of the assessment
The PhVWP concluded that the SmPCs (sections 4.4 and 4.5) and PLs for products containing valproic acid or sodium valproate should be expanded in accordance with the latest information included in the SmPCs and PLs for carbapenems.

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