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Pharmacovigilance Working Party (PhVWP)

September 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its September 2010 plenary meeting on 20-22 September 2010.

Safety concerns

The positions agreed by the PhVWP for non-centrally authorised medicinal products form recommendations to Member States and the related discussions of the PhVWP are summarised below in accordance with the PhVWP publication policy. 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 other CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the CHMP Monthly Report (http://www.ema.europa.eu, go to: about us/Committees/Committees meeting reports/CHMP).

Benzydamine – Risk of adverse reactions after incorrect oral intake

Benzydamine powder is intended for the preparation of solutions for external gynaecological use only and its incorrect oral intake may cause systemic adverse reactions

The PhVWP reviewed data from Italy indicating an increased number of reports of benzydamine powder being taken orally by mistake. Benzydamine powder is intended for the preparation of solutions for external gynaecological use and is available in Italy as a non-prescription medicine. The powder should not be administered orally and adverse reactions arising from the oral intake may affect the gastro-intestinal, central-nervous and cardio-vascular systems. The PhVWP noted that the Italian competent authorities decided to request the concerned marketing authorisation holders to change the packaging, summary of product characteristics and package leaflets to strengthen instructions on the correct route of administration of the Italian medicinal products containing benzydamine powder for the preparation of solutions for external gynaecological use. The PhVWP concluded that the need for similar risk

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minimisation measures should also be considered in other Member States where such products are marketed and where there is evidence of the occurrence or the potential of medication errors (see Annex 1 for the Summary Assessment Report).

Lamotrigine – Risk of aseptic meningitis

Current EU product information including aseptic meningitis as an adverse reaction of lamotrigine confirmed as consistent with current evidence

Following the recent announcement by the US Food and Drug Administration that lamotrigine can cause aseptic meningitis, the PhVWP noted that the summaries of product characteristics (SmPCs) and package leaflets (PLs) for lamotrigine-containing medicines authorised in the EU already include the adverse reaction of aseptic meningitis but reviewed the available evidence to consider whether any new data had emerged which would require an update of the current product information in this respect. Having reviewed the data, including those provided by the marketing authorisation holder for the originator product, the PhVWP concluded that the limited new data do not add to existing knowledge and that therefore the current product information for lamotrigine-containing medicines authorised in the EU remains adequate. Aseptic meningitis is included in the current SmPC as an adverse reaction of unknown frequency in section 4.8 and also listed in the PL, reflecting the available knowledge. No further action was therefore deemed necessary (see Annex 2 for the Summary Assessment Report).

Tamoxifen – Risk of reduced therapeutic response in patients who are poor CYP2D6 metabolisers or use medicines inhibiting CYP2D6

Avoid use of potent CYP2D6 inhibitors during tamoxifen treatment whenever possible and be aware that poor CYP2D6 metabolisers may respond less well to tamoxifen treatment

Following the publication of studies in the medical literature, the PhVWP conducted a review of the risk of reduced therapeutic response to tamoxifen in breast cancer patients who are poor CYP2D6 metabolisers or who use medicines inhibiting the cytochrome P450 CYP2D6 enzyme. Based on this review, the PhVWP concluded upon recommendations for the summaries of product characteristics (SmPCs) and package leaflets (PLs) for medicines containing tamoxifen, to highlight the possible reduction in therapeutic response to tamoxifen in poor CYP2D6 metabolisers and to warn against using potent CYP2D6 inhibitors during tamoxifen treatment whenever possible (see Annex 3 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.

Guidelines and general matters

Below is a summary of the main discussions on guidelines and other general matters of an organisational, regulatory or methodological nature.

Election of PhVWP Vice-Chairperson

The PhVWP elected A Spooner, the Irish PhVWP Member, as new Vice-Chairperson of the PhVWP in accordance with its mandate and rules of procedures.

New legislation for pharmacovigilance in the European Union

The PhVWP noted that on 22 September 2010, the European Parliament (EP) approved new legislation to strengthen pharmacovigilance in the EU. Subsequently, the PhVWP held its first discussion to plan its contributions to the implementation of the new legal provisions. The new legislation will come into force 18 months after its publication in the Official Journal. Interested readers are referred to the website of the EP: http://www.europarl.europa.eu/news/expert/infopress_page/066-83196-263-09-39-911-20100921IPR83194-20-09-2010-2010-false/default_en.htm.

1st EMA Scientific Workshop on Nanomedicines on 2-3 September 2010

The PhVWP took note of the discussions at the 1st Scientific Workshop on Nanomedicines organised by the agency on the benefits and challenges arising from the application of nanotechnologies to medicines with a view to preparing for the evaluation of future nanomedicines. Interested readers are referred to the agency website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001108.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true.

Regulatory abbreviations

CHMP – Committee for 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

PASS – post-authorisation safety study

PhVWP – CHMP Pharmacovigilance Working Party

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 September 2010

Benzydamine – Risk of adverse reactions after incorrect oral intake

Key message

Benzydamine powder is intended for the preparation of solutions for external gynaecological use only and its incorrect oral intake may cause systemic adverse reactions

Safety concern and reason for current safety review

From December 2009 to early January 2010, the poisons information centres in Milan and Pavia, Italy, recorded a considerable increase in the number of reported medication errors with the use of TANTUM ROSA, a medicine containing 500 mg benzydamine hydrochloride powder in sachets for the preparation of solutions for external gynaecological use. The medication errors mostly related to the wrong route of administration, i.e. oral intake instead of external use. In a few cases, the product was accidentally taken orally instead of another medicine. The increase of erroneous oral intake was suspected to be in association with the medicinal product recently being re-classified from prescription-only to non-prescription medicine and a subsequent advertising campaign in December 2009. Risk minimisation measures were put in place immediately by the Italian Ministry of Health, which required the modification of the advertising material to strengthen the information on the correct route of administration.

The reported reactions of erroneous oral intake mainly concerned the gastro-intestinal system (in particular the oropharynx), but also the central-nervous and the cardio-vascular systems.

Given this increase in reported medication errors, a review was undertaken by the Italian competent authorities and the PhVWP.

Clinical setting

Benzydamine is a non-steroidal anti-inflammatory agent for external use in painful and inflammatory conditions of the skin and mucosa, in areas such as the mouth and the vagina. Only small amounts of benzydamine are systemically absorbed after external administration.

Information on the data assessed

The Italian competent authorities requested the poisons information centre of Milan to perform an assessment of the medication errors reported to them for benzydamine and to monitor the impact of the risk minimisation measures. In addition, a review of the medical literature was performed [1-4].

According to pharmacokinetic data in the literature, 64% of ingested benzydamine is absorbed within 1 hour and full absorption is completed within 4 to 6 hours; 50% is excreted as benzydamine in the urine and 50% is broken down in the liver.

Literature data on oral intake of high doses and overdoses ($\geq$ 500 mg) of benzydamine hydrochloride indicate that it can cause symptoms effecting the central-nervous system, such as excitement, muscle weakness, somnolence (chronic drowsiness), or delirium (an acute state of confusion) as well as visual and tactile hallucinations.

A published study of 724 cases of oral intake of gynaecological products containing benzydamine powder reported to the Spanish poisons control centre between 1991 and 2003 found that the medication errors were commonly due to the misinterpretation of the product information regarding the route of administration [3].

Outcome of the assessment

Based on the assessment of the medication errors reported for benzydamine, the monitoring of the impact of the risk minimisation measures and the literature review, the PhVWP considered that:

- the use of benzydamine-containing medicines for gynaecological use is associated with an increased frequency of medication errors due to oral instead of correct external administration;
- the majority of cases occur with powder contained in sachets for the preparation of a gynaecological solution;
- despite a decrease in the number of cases reported after the modification of the advertising material, the number of cases remained high compared to previous years.

In the light of these considerations, the Italian competent authorities decided to request the concerned marketing authorisation holders to alter the colour of the packaging and to strengthen the information on the correct route of administration in the summary of product characteristics and package leaflets of Italian medicinal products containing benzydamine powder for the preparation of solutions for external gynaecological use.

The PhVWP concluded that the need for similar risk minimisation measures should also be considered in other Member States where such products are marketed and where there is evidence of the occurrence or the potential of medication errors.

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Annex 2

Summary Assessment Report of the PhVWP September 2010

Lamotrigine – Risk of aseptic meningitis

Key message

Current EU product information including aseptic meningitis as an adverse reaction of lamotrigine confirmed as consistent with current evidence

Safety concern and reason for current safety review

Recently, the US Food and Drug Administration (FDA) informed the public that lamotrigine can cause aseptic meningitis [1]. Since 2008, the product information for lamotrigine-containing medicines authorised in the EU has included aseptic meningitis as an adverse reaction. Given the announcement by the FDA, the PhVWP reviewed whether there was any new data warranting an update of the current EU product information in this respect.

Meningitis is an inflammation of the protective membranes covering the brain and spinal cord. Aseptic means that it is not caused by bacterial infection. If symptoms of meningitis occur, it is important to rapidly diagnose the underlying cause so that treatment can be promptly initiated, and any causative factor addressed.

Clinical setting

Lamotrigine is indicated in the EU for the treatment of epilepsy and the prevention of depressive episodes in bipolar disorder.

Information on the data assessed

The marketing authorisation holder for the originator product informed the competent authorities in the EU that an analysis of all cases of aseptic meningitis reported for lamotrigine had been submitted to the FDA upon their request. The analysis detailed all cases of meningitis up to May 2007. These were the same 31 cases that supported the change to the EU product information in 2008. The marketing authorisation holder provided the competent authorities in the EU with an addendum to this analysis, detailing 9 new cases reported between May 2007 and 17 September 2009, and supplemented it later by an update of 5 July 2010, bringing the total to 44 reported cases. The marketing authorisation holder considered whether an update to the current EU product information was warranted and concluded that the new cases were similar in nature to those collected up to May 2007 and did not add anything to the previous EU assessment or change the conclusions reached at that time.

Outcome of the assessment

The PhVWP reviewed the data from the marketing authorisation holder. The review showed that 42 reports of the 44 case reports had already been submitted to the competent authorities in the EU in the last periodic safety update report and had been assessed as part of the procedure for the renewal of marketing authorisation in the EU. The PhVWP considered that the data did not add to existing knowledge which would require changes to the product information and concluded that the current mention of aseptic meningitis as an adverse reaction of unknown frequency in section 4.8 of the

summary of product characteristics and its description in language suitable for patients in the package leaflet as currently presented remains adequate. No further action was therefore deemed necessary.

References

[1] FDA Drug Safety Communication: Aseptic meningitis associated with use of Lamictal (lamotrigine). Rockville, MD: US Food and Drug Administration; 12 August 2010. Available under http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm221847.htm (last accessed on 22 September 2010).

Annex 3

Summary Assessment Report of the PhVWP September 2010

Tamoxifen – Risk of reduced therapeutic response in patients who are poor CYP2D6 metabolisers or use medicines inhibiting CYP2D6

Key message

Avoid use of potent CYP2D6 inhibitors during tamoxifen treatment whenever possible and be aware that poor CYP2D6 metabolisers may respond less well to tamoxifen treatment

Safety concern and reason for current safety review

Tamoxifen is extensively broken down in the body through the process of metabolism to form several intermediate products known as metabolites which have similar or enhanced pharmacological activity in comparison to tamoxifen. The formation of active metabolites, e.g. endoxifen, is predominantly mediated by the cytochrome P450 CYP2D6 enzyme (hereafter referred to as CYP2D6).

Recently, a number of studies have been published in the medical literature on the potential effect of genetic variants of CYP2D6 on the therapeutic responses of patients to tamoxifen in the treatment of breast cancer.

The studies gave rise to the concern that patients with inherited non-functional alleles of the gene coding for CYP2D6 or patients who are concomitantly treated with medicines inhibiting CYP2D6, i.e. blocking the action of this enzyme, might not be suitable for adjuvant tamoxifen therapy, due to reduced concentrations of those metabolites of tamoxifen that bind most strongly with the oestrogen receptor expressed by the breast cancer.

Therefore, the PhVWP reviewed the available evidence in this respect.

Clinical setting

Tamoxifen is a selective oestrogen receptor modulator indicated for palliative and adjuvant treatment of oestrogen receptor-positive breast cancer, in both pre- and post-menopausal women. Oestrogen receptor-positive breast cancer cells grow in response to the hormone oestrogen. Tamoxifen works by attaching to the receptors for oestrogen on the surface of cancer cells so that these cells are not stimulated to grow by oestrogen and the growth of the cancer is reduced.

Information on the data assessed

Following the studies published in the medical literature, a list of questions was forwarded to the marketing authorisation holder of the originator product requesting its views, in particular on the risk of reduced therapeutic response to tamoxifen in 1) patients who are poor CYP2D6 metabolisers, 2) patients who are concomitantly treated with potent CYP2D6 inhibitors, and 3) in patients with different ethnicity regarding CYP2D6 polymorphisms.

While the assessment of the responses from the marketing authorisation holder by the PhVWP was ongoing, new studies were published.

The PhVWP reviewed all currently available data and the limitations and controversial interpretations of the published studies [1-14] were considered. Also, the views of the CHMP Pharmacogenomics Working Party (PGWP) and the Scientific Advice Group (SAG) on Oncology were sought.

Outcome of the assessment

The PhVWP considered the following:

Effect of tamoxifen in poor CYP2D6 metabolisers

A study [1] including 1325 patients from US and German cohorts (95.4% post-menopausal) with hormone receptor-positive non-metastatic breast cancer at diagnosis and treated with tamoxifen and no chemotherapy afterwards showed a significantly increased risk of breast cancer recurrence for poor CYP2D6 metabolisers (several alleles were analysed in the study: CYP2D6*3, *4 and *5 (HR 1.90, 95% CI 1.10-3.28) and heterozygous metabolisers (HR 1.40, 95% CI 1.04-1.90) compared to extensive metabolisers).

Additional studies including those providing contradictory results were assessed. Several of the studies indicated that poor CYP2D6 metaboliser status may be associated with a reduced response [2-6]. The few studies [7-9] in Caucasian populations showing contradictory results (n=3 from 2005 or 2007) may have been confounded by e.g. the higher tamoxifen dose used, small number of poor CYP2D6 metabolisers or limited number of CYP2D6 mutations analysed, all of which may reduce the ability to demonstrate a reduced response of tamoxifen in patients with poor CYP2D6 metaboliser status.

In the most recently published large study [10], which included patients with invasive breast cancer from SEARCH (Studies of Epidemiology and Risk Factors in Cancer Heredity; 3155 patients were treated with tamoxifen and 3485 patients did not receive tamoxifen), there was some evidence that the poor metaboliser variant CYP2D6*6 (a more uncommon variant with a mean allele frequency (MAF) = 0.01) was associated with decreased breast cancer-specific survival. However, CYP2D6*4 (the most common poor metaboliser variant with MAF = 0.20) was not shown to be associated with poorer clinical outcomes, in contrast to the previous findings [1]. Methodological issues were discussed on the genotyping quality taking into account the Hardy-Weinberg equilibrium.

Variability of frequency of the CYP2D6 poor metaboliser variants in different ethnic populations

The impact of the intermediate metaboliser allelic variants (e.g.*10*10 for the Chinese, Japanese and Korean populations) on the clinical effect of tamoxifen was discussed. Large variability between different studies was observed and no firm conclusions could be drawn.

Effect of tamoxifen in patients treated with potent CYP2D6 inhibitors

Another study [11] referred to data from a population-based cohort study on selective serotonin reuptake inhibitors (SSRIs) and breast cancer mortality in women receiving tamoxifen. In this study, data from a healthcare record database in Ontario, Canada, were used to evaluate the clinical consequences for women with breast cancer who were treated with both tamoxifen and an SSRI. It was found that the risk of death from breast cancer increased with the length of concomitant treatment with paroxetine, a potent inhibitor of CYP2D6, but not with other SSRIs. For example, if women used paroxetine for 41% of the time that they took tamoxifen, one additional death from breast cancer occurred within five years after stopping tamoxifen for every 19.7 (95% CI 12.5-46.3) women treated. The proportion of time on tamoxifen with overlapping use of paroxetine of 25%, 50%, and 75% was associated with 24%, 54%, and 91% increases in the risk of death from breast cancer.

In a more recent study [12], no evidence was found for a decrease in efficacy with the co-administration of CYP2D6 inhibitors and tamoxifen. However, the authors, considering the results from

the available studies and the strong mechanistic model, concluded that their results should be interpreted with caution.

Overall considerations

Based on all the evidence, the PhVWP considered that the available published data, mainly on post-menopausal women treated for breast cancer with tamoxifen, suggest that CYP2D6 polymorphism status may be associated with different therapeutic response of patients to tamoxifen. Poor CYP2D6 metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of poor CYP2D6 metabolisers have not been fully understood. The available data at present have not clearly shown the clinical utility of CYP2D6 testing to predict tamoxifen efficacy and clinical outcome. There is insufficient evidence at present to recommend genotyping patients before starting tamoxifen treatment.

Additionally, the PhVWP noted that pharmacokinetic interactions with CYP2D6 inhibitors were described in the medical literature, showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen [13]. Reduced efficacy of tamoxifen was reported with concomitant use of some SSRI antidepressants (e.g. paroxetine) [11]. However, in other studies, a decrease in efficacy of tamoxifen with the co-administration of CYP2D6 inhibitors was not evident [12]. As a reduced effect of tamoxifen cannot be excluded, particularly in the context of the pharmacokinetic data and mechanistic plausibility, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cincalet or buproprion) should be avoided whenever possible [14].

Therefore, the PhVWP concluded upon recommendations for the summaries of product characteristics and package leaflets for medicinal products containing tamoxifen to highlight the possible reduction in therapeutic response to tamoxifen in poor CYP2D6 metabolisers and to warn against using potent CYP2D6 inhibitors during tamoxifen treatment whenever possible.

References

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