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Pharmacovigilance Working Party (PhVWP)

June 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its June 2011 plenary meeting on 20-22 June 2011.

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 CHMP monthly report (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000190.jsp).

Beta-blockers for ophthalmic use – Risk of systemic adverse reactions

The PhVWP recommends harmonisation of product information across the EU for ophthalmic beta-blockers with regard to systemic adverse reactions.

The PhVWP identified major differences in the summaries of product characteristics of beta-blockers authorised in the EU for ophthalmic use regarding the information on possible systemic effects between the different carteolol-containing ophthalmic products as well as in comparison to other ophthalmic beta-blockers.

After reviewing all available data, the PhVWP recommended core safety information for the summaries of product characteristics (SmPCs) of medicinal products containing beta-blockers (single substance

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and combination products) for ophthalmic use[1] based on agreed principles (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the final wording to be included in the 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.

The recommendations from the PhVWP were also transmitted to the CHMP for consideration for relevant centrally authorised products, i.e. products containing timolol in combination with bimatoprost (GANFORT), brinzolamide (AZARGA) and travoprost (DUOTRAV), and interested readers are referred to the agency's website (http://www.ema.europa.eu) for upcoming revised SmPCs and PLs.

GEMCITABINE ACTAVIS – Risk of adverse reactions due to increased alcohol concentration after reconstitution error

Alcohol-related adverse reactions may occur with GEMCITABINE ACTAVIS due to reconstitution errors. The product information will be updated to emphasise the need to dilute the concentrate correctly before infusion.

The PhVWP reviewed cases of alcohol-related adverse reactions occurring in Dutch hospitals with the use of GEMCITABINE ACTAVIS. The PhVWP considered these reactions to be due to reconstitution errors resulting in increased alcohol concentration of the final solution being administered. The PhVWP concluded that the product information should be updated to emphasise the need to dilute the concentrate correctly before infusion and that the marketing authorisation holder should be asked to monitor adverse reaction reports suggestive of reconstitution errors (see Annex 2 for the Summary Assessment Report).

Hydrochlorothiazide – Use during breast-feeding

Using hydrochlorothiazide during breast-feeding is not recommended but available evidence does not justify a contraindication.

The PhVWP recognised the need for harmonised product information regarding the use of hydrochlorothiazide during breast-feeding. Following a review of the medical literature and current product information, the PhVWP concluded that the product information for all hydrochlorothiazide-containing medicinal products (single substance and combination products) should reflect that hydrochlorothiazide is excreted into human milk in small amounts and that thiazides in general, when given at high doses, can inhibit the milk production by causing intense diuresis and that therefore the use of hydrochlorothiazide during breast-feeding is not recommended and doses should be kept as low as possible. The PhVWP also concluded that a contraindication during breast-feeding is not justified based on the information available (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the final wording to be included in 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.

[1] The active substances included in this review were befunolol, betaxolol, carteolol, levobunolol, metipranolol and timolol.

Testosterone 10% for topical use – Risk of virilisation in children after exposure through interpersonal skin contact

Children may develop virilisation after exposure to testosterone through interpersonal skin contact with a person using testosterone topically as a magistral preparation at concentrations higher than authorised, e.g. 10%.

The PhVWP reviewed a concern arising from five Belgian case reports of virilisation in young children where the father had used topically a magistral preparation of testosterone 10% gel. The PhVWP considered that the package leaflets for medicinal products, authorised in the EU, with 1 to 2% testosterone for topical use include a warning on interpersonal transfer and concluded that at this time no further action seems to be required for the authorised products. With regard to magistral preparations of testosterone at higher concentrations, healthcare professionals in Belgium will be informed about the risk of virilisation in children after exposure through interpersonal skin contact by means of appropriate communication (see Annex 4 for the Summary Assessment Report).

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.

Meetings of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in June 2011

The PhVWP contributed to the preparations of the latest ICH meetings, in particular with regard to the ongoing revision of the ICH-E2C Guideline on periodic reporting, and was updated with information on the progress achieved. Interested readers are referred to the ICH website http://www.ich.org/.

Guide on the interpretation of spontaneous case reports of suspected adverse reactions to medicines

The PhVWP finalised guidance on how to interpret information on case reports of suspected adverse reactions to medicines, which may be used by those seeking access to such data or those generally interested in the safety of medicines. The guidance will be published shortly under: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000456.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac05801ae8fb.

Study of influential stakeholders' expectations and attitudes regarding benefit-risk communication by the European Medicines Agency

The PhVWP was provided with the final report on a study looking into the expectations and attitudes of the agency's stakeholders on its communication on the benefit-risk balance of medicines. The agency had invited an independent expert, Dr Frederic Bouder from King's College London, now Maastricht University, to conduct this study, given the agency's commitment to improving its communication with patients, healthcare professionals and the general public.

The PhVWP had previously discussed the study results with Dr Bouder and welcomed the insights gained as well as his recommendations. The agency is considering his recommendations in the light of the new pharmacovigilance legislation and some of them are already being implemented.

To access the study report, interested readers are referred to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000456.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac05801ae8fb.

Driving under the Influence of Drugs, Alcohol and Medicines - The Integrated Project DRUID under the European Commission's 6th Framework Programme

The objective of DRUID, a project funded by the European Commission under the 6th Framework Programme, is to give scientific support to the EU transport policy regarding road safety by developing guidelines and measures to reduce impaired driving under the influence of alcohol, illicit drugs and medicines.

Members of the project consortium approached the PhVWP for its contribution in relation to the development of a classification system of medicines for fitness to drive and a corresponding labelling scheme. The PhVWP engaged in an interaction throughout this development and now finalised its contribution. The PhVWP agreed that any information on the influence of medicines on driving ability should be simple and helpful to the patient, and therefore be reflected in the package leaflet (PL). The PhVWP recommended including in the PL a two-tier risk classification system differentiating between medicinal products with a potential for relevant influence on driving (moderate or major influence) and medicinal products without a potential for relevant influence (no or minor influence). However, the PhVWP acknowledged activities at the level of Member States to reinforce the awareness of patients on the effects of medicines on driving abilities. Therefore, the PhVWP recognised that this two-tier risk classification system could be further divided to include a maximum of four categories at the discretion of Member States. The inclusion of further categories would remain consistent with the current EU Guideline on Summary of Product Characteristics (see http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm). The PhVWP also recommended that the use of an alerting pictogram on the product packaging should remain optional.

The PhVWP transmitted their recommendations to the members of the project consortium, which will deliver its final report to the European Commission in June 2011. Interested readers are referred to the DRUID website: http://www.druid-project.eu/cln_007/Druid/EN/home/homepage__node.html?__nnn=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 – periodic safety update report

RMP – risk-management plan

SmPC – summary of product characteristics

Annex 1

Summary Assessment Report of the PhVWP June 2011

Beta-blockers for ophthalmic use – Risk of systemic adverse reactions

Key message

Harmonisation of product information across the EU for ophthalmic beta-blockers with regard to systemic adverse reactions is recommended by the PhVWP in line with agreed principles.

Safety concern and reason for current safety review

During the assessment of a recent periodic safety update report for the beta-blocker carteolol, major differences in the summaries of product characteristics (SmPCs) of beta-blockers for ophthalmic use regarding the information on possible systemic effects were identified between the different carteolol-containing products as well as in comparison to other beta-blockers for ophthalmic use authorised in the EU.

As a consequence, the PhVWP agreed to review the topic in the context of a class review of the potential systemic adverse reactions of all ophthalmic medicines containing a beta-blocker as a single substance preparation or a preparation containing a beta-blocker in combination with other active substances. The aim was to agree core safety information for the SmPCs and the package leaflets of ophthalmic beta-blockers.

The active substances included in this class review were befunolol, betaxolol, carteolol, levobunolol, metipranolol and timolol.

Clinical setting

Ophthalmic beta-blockers have been widely used in the treatment of glaucoma and ocular hypertension for more than 20 years.

Glaucoma is a common disease, especially in the older population. The number of persons estimated to be blind as a result of primary glaucoma is 4.5 million worldwide, accounting for slightly more than 12% of blindness globally. Primary therapy for these patients is aimed at lowering the intraocular pressure (IOP).

Information on the data assessed

The assessment of systemic adverse reactions after local administration of beta-blockers for ophthalmic use included data from the medical literature, spontaneous reports on suspected adverse reactions and safety data available in Member States of the EU.

These data included responses to an information request circulated to Member States, data query results from EudraVigilance (the EU regulatory network database for adverse reaction case reports), published epidemiological, clinical and pharmacokinetic studies [1-78] and the assessment reports, together with the core safety profiles, agreed by the CMDh/PhVWP Working Group on Periodic Safety Update Report Worksharing for betaxolol, carteolol, levobunolol, timolol, timolol+brimonidine, timolol+dorzolamide and timolol+ latanoprost. The assessment was limited by the fact that many of the published studies date from before 2000.

Outcome of the assessment

After reviewing all available data, the PhVWP agreed to recommend core safety information for the SmPCs of ophthalmic beta-blockers based on the following principles:

- Topically applied ophthalmic medicines can, to various extents, be absorbed directly into the blood stream, via the naso-lachrymal duct, thus avoiding first-pass metabolism in the liver. Very often sufficient amount of these medicines passes directly into the systemic circulation, thereby causing unwanted systemic adverse reactions. In the case of beta-blockers, such adverse reactions may affect the cardiovascular, respiratory, nervous and endocrine systems.

  After administration, approximately 80% of the eye drops get drained through the naso-lachrymal duct within 15 to 30 seconds and may get absorbed systemically. To help limit this drainage through the naso-lachrymal duct, a recommendation for naso-lachrymal occlusion or closing the eyelids for two minutes should be included in SmPC section 4.2. To strengthen the importance of manoeuvres for limitation of systemic absorption it was proposed to include cross-references in SmPC sections 4.4 and 4.6.

- It was agreed that the contraindications for ophthalmic products in SmPC section 4.3 should be in line with contraindications for systemic beta-blockers used for the treatment of hypertension and other cardiovascular disorders, taking into consideration the pharmacokinetics of ophthalmic medicines.

  Contraindications should not limit the use of ophthalmic products by patients with mild to moderate form of cardiovascular disorders or bronchial hyperactivity.

- Ophthalmic beta-blockers could worsen several disturbances/disorders such as bronchial, cardiac and vascular diseases, thus this message should be strengthened in SmPC section 4.4. Patients with these diseases should be treated with caution and should be monitored for signs of deterioration of these diseases.

- Ophthalmic beta-blockers may block systemic beta-agonist effects, e.g. of adrenaline. This is important during anaesthesia, treatment of anaphylactic reactions and also for diabetic patients as signs of hypoglycaemia can be masked.

- Beta-blockers used for treatment of glaucoma differ in their pharmacological properties, in particular selectivity, intrinsic sympathomimetic activity and local anaesthetic activity.

- Only slight differences between substances can be seen: for instance the cardioselective beta-blocker betaxolol is associated with a reduced risk of adverse effects on bronchial function when compared with the non-selective beta-blockers. However, this selectivity is not absolute. The proposed contraindication and associated warnings with respect to patients with asthma and chronic obstructive pulmonary disease (COPD) reflect this relative difference in pharmacodynamic effects. For timolol, systemic adverse reactions can be potentiated when used concomitantly with P450 CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine), because timolol is metabolised by the cytochrome P450 CYP2D6 enzyme. This should be highlighted in SmPC section 4.5.

- All other information included in SmPC sections 4.4, 4.5, 4.6 and 4.8 should be presented as class effects seen with other beta-blockers regardless of whether the effect has been described or reported for a particular active substance. Data from clinical studies with the particular medicinal product can be presented in the first part of section 4.8.

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Annex 2

Summary Assessment Report of the PhVWP June 2011

GEMCITABINE ACTAVIS – Risk of adverse reactions due to increased alcohol concentration after reconstitution error

Key message

Alcohol-related adverse reactions may occur with GEMCITABINE ACTAVIS due to reconstitution errors. The product information will be updated to emphasise the need to dilute the concentrate correctly before infusion.

Safety concern and reason for current safety review

By March 2011, the Medicines Evaluation Board of the Netherlands had received several adverse reaction reports after administration of GEMCITABINE ACTAVIS, potentially related to the alcohol content of the insufficiently diluted solution. These reports originated from two Dutch hospitals which recently started using GEMCITABINE ACTAVIS in place of other gemcitabine-containing products.

Both hospitals reported similar adverse reactions. 9 reactions were reported from 25 administrations in one hospital, and 2 reactions from 6 administrations in the other hospital. The reported adverse reactions were pain during the infusion, nausea, malaise, dizziness and erythema.

The PhVWP agreed to review the safety concern emerging from this data.

Clinical setting

Gemcitabine is a medicine used against various kinds of cancer.

Information on the data assessed

The review was based on the adverse reaction reports on the concerned patients.

Outcome of the assessment

The data indicated that the adverse reactions reported for GEMCITABINE ACTAVIS were due to the insufficient dilution of the concentrate, leading to a higher concentration in alcohol of the final solution.

The PhVWP concluded that the product information for GEMCITABINE ACTAVIS should be updated to emphasise the need to dilute the concentrate correctly before infusion and the marketing authorisation holder should be asked to monitor adverse reaction reports suggestive of reconstitution errors.

Annex 3

Summary Assessment Report of the PhVWP June 2011

Hydrochlorothiazide – Use during breast-feeding

Key message

Using hydrochlorothiazide during breast-feeding is not recommended but available evidence does not justify a contraindication.

Safety concern and reason for current safety review

Previously, the PhVWP had agreed recommendations on the use of some antihypertensive medicines in pregnancy and breast-feeding, namely for angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists regarding pregnancy and breast-feeding and for hydrochlorothiazide regarding pregnancy. These recommendations were subsequently published by the CMD(h). However, recommendations on the use of hydrochlorothiazide during breast-feeding were lacking. Since many combination products containing hydrochlorothiazide and an ACE inhibitor or an angiotensin II receptor antagonist are authorised in the EU, the PhVWP recognised the need for harmonised product information regarding the use of hydrochlorothiazide during breast-feeding.

Breast-feeding is recognised to provide important health benefits for the infant and mother. However, milk production (lactation) may be affected by thiazide diuretic medicines, and hydrochlorothiazide is excreted in small amounts into human milk. The PhVWP therefore considered that adequate product information was needed to guide healthcare professionals and mothers when deciding on the use of hydrochlorothiazide during breast-feeding.

Clinical setting

Hydrochlorothiazide is a thiazide diuretic which acts by inhibiting the reabsorption of sodium into the cortical diluting segment of renal tubules. It increases the excretion of sodium and chloride in urine and, to a lesser extent, potassium and magnesium, thereby increasing urinary output and exerting an antihypertensive effect.

Information on the data assessed

The PhVWP reviewed information from the medical literature [1-5] and the summaries of product characteristics (SmPCs) for the combination products ramipril+hydrochlorothiazide and valsartan+hydrochlorothiazide, which had been the subject of Article 30 referrals [6].

Outcome of the assessment

The PhVWP concluded that the SmPCs and package leaflets for all hydrochlorothiazide-containing medicinal products (single substance and combination products) should reflect the fact that hydrochlorothiazide is excreted into human milk in small amounts and that thiazides in general, when given at high doses, can inhibit milk production by causing intense diuresis, that the use of hydrochlorothiazide during breast-feeding is therefore not recommended, and that if hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

The PhVWP also concluded that a contraindication of its use during breast-feeding is not justified as the information available suggests that the amount of hydrochlorothiazide excreted into human milk is not substantial. In addition, adverse effects in breast-fed infants have not been reported up to now.

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Diovan_Comp/human_referral_000004.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024e9a

Annex 4

Summary Assessment Report of the PhVWP June 2011

Testosterone 10% for topical use – Risk of virilisation in children after exposure through interpersonal skin contact

Key message

Children may develop virilisation after exposure to testosterone through interpersonal skin contact with a person using testosterone topically as a magistral preparation at concentrations higher than authorised, e.g. 10%.

Safety concern and reason for current safety review

The Belgian Federal Agency for Medicines and Health Products (FAMHP) received, by the end of 2010, 5 case reports of virilisation in young children where the father had applied a magistral preparation of testosterone 10% gel for topical use.

There is a concern about the risk of inadvertent interpersonal transfer of testosterone through skin-to-skin contact with somebody using that gel. Although some testosterone penetrates the skin, after the evaporation of the alcohol contained in the preparation, testosterone is left on the skin with the potential to be transferred to another person.

The PhVWP therefore agreed to review this safety concern.

Clinical setting

Testosterone gels at concentrations of 1 to 2% are authorised in Belgium and other Member States for treatment of hypogonadism in men after biological confirmation of a testosterone deficiency.

The recommended application sites are the abdomen, the shoulders and upper arms and the inner thighs. Users are also advised to wash their hands after application, to cover the exposed skin with clothing or to take a shower prior to physical contact.

The recommended starting dose for these testosterone gels is 50 or 60 mg testosterone per day. The average male testosterone production rate is estimated to be between 5 and 10 mg per day [4].

This review related to magistral preparations of testosterone gels at concentrations higher than those authorised. Magistral preparations are medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient.

Information on the data assessed

The PhVWP reviewed the cases reported in Belgium and relevant information from the medical literature [1-9].

Outcome of the assessment

The PhVWP considered that the reported cases of virilisation in children are a direct consequence of the use of testosterone gel by their father. After skin-to-skin contact with the father, the children absorbed testosterone and developed sexual symptoms associated with high testosterone blood levels. In the

reported cases, the testosterone gels were highly concentrated (10%) compared to the authorised concentrations of 1 to 2%.

Since the cases were only reported in Belgium, no suggestions for EU-wide measures were put forward. A warning on interpersonal transfer is already included in the package leaflets (PLs) for testosterone-containing products authorised in the EU. However, magistral preparations are specifically prepared for individual patients and no PL is available. Healthcare professionals in Belgium will be informed, by means of appropriate communication, of the risk of virilisation in children after exposure to testosterone through interpersonal skin contact with a person using a magistral preparation of testosterone at high concentration, e.g. 10%.

At this time, the PhVWP concluded that no further action seems to be required for the authorised testosterone-containing medicinal products for topical use since the product information adequately addresses this safety concern.

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