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Pharmacovigilance Working Party (PhVWP)

July 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its July 2010 plenary meeting on 19-21 July 2010.

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, go to: about us/Committees/Committees meeting reports/CHMP).

Camphor for external or inhaled use – Risk of toxic effects after accidental oral intake

Accidental oral intake of camphor (≥ 400mg) requires consultation with a physician for symptomatic treatment of toxic effects (vomiting should not be induced)

The PhVWP concluded upon recommendations for the summaries of product characteristics (SmPCs) and package leaflets (PLs) for medicinal products for topical or inhaled use containing 400mg or more camphor in a single package regarding toxic effects following accidental oral intake (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 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.

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Isotretinoin for oral use – Risk of erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis

Patients should stop isotretinoin if a serious skin rash develops and see their physician immediately, as this could mark the onset of a potentially life-threatening skin reaction (i.e. erythema multiforme, Stevens Johnson syndrome or toxic epidermal necrolysis)

The PhVWP conducted a new review of three types of severe skin reaction with isotretinoin on the basis of new evidence that has become available after the last PhVWP review (see PhVWP Monthly Report March 2010). Isotretinoin is authorised as a treatment for severe acne.

Based on the available data, the PhVWP concluded that a causal association between isotretinoin and the reactions Stevens Johnson syndrome and toxic epidermal necrolysis cannot be excluded and that these skin reactions should also be included in the summaries of product characteristics (SmPCs) and package leaflets (PLs) of oral isotretinoin-containing products, in addition to erythema multiforme (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.

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.

Medical Dictionary for Drug Regulatory Activities (MedDRA) – List of Important Medical Event Terms (IME)

The PhVWP heard an update on the development of the list of Important Medical Event Terms (IME) and was invited to submit comments.

This IME list aims to facilitate the classification of suspected adverse reactions as well as case assessment and the analysis of aggregated data. It is developed under the coordination of the EudraVigilance Expert Working Group (EV-EWG). Interested parties may contribute to the development through participation in the online survey, open until 26 October 2010 and accessible under http://eudravigilance.emea.europa.eu/human/textforIME.asp.

The IME list sources terms from the Medical Dictionary for Drug Regulatory Activities (MedDRA). For more information on MedDRA, interested readers are referred to http://www.meddramsso.com.

European Programme in Pharmacovigilance and Pharmacoepidemiology (Eu2P)

The PhVWP prepared comments on training needs as a contribution to the European Programme in Pharmacovigilance and Pharmacoepidemiology (Eu2P). The Eu2P project consortium currently develops training courses for specialists and non-specialists in the area of safety surveillance of medicines and its underlying methods. The project is funded by the Innovative Medicines Initiative Joint Undertaking, a public-private partnership between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union represented by the European Commission. The European Medicines Agency is part of the consortium. For more information on Eu2P, interested readers are referred to http://www.eu2p.org.

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 July 2010

Camphor for external or inhaled use – Risk of toxic effects after accidental oral intake

Key message

Accidental oral intake of camphor (≥ 400mg) requires consultation of a physician for symptomatic treatment of toxic effects (vomiting should not be induced).

Safety concern and reason for current safety review

During a procedure to vary the marketing authorisation for a camphor-containing ointment in Portugal, questions arose on the absence of advice in the product information on the risk of accidental oral intake and the management of such overdose. This triggered a safety review in this respect for all camphor-containing medicinal products in Portugal for external or inhaled use.

Oral intake of camphor may lead to toxic exposure, with a rapid onset of the toxic, potentially fatal effects. Its major toxic effect is convulsions. The data show that this risk is more common in children below six years of age.

Clinical setting

Externally, camphor is used as a rubefacient, anti-pruritic, surface anaesthetic and antibacterial agent. It is also used in inhaled preparations as a decongestant and expectorant against the symptoms of the common cold.

Information on the data assessed

The assessment was performed by analysing the available data by formulation and total quantity of camphor per package. The available data included a risk assessment from the Portuguese poison control centre.

Only a small number of camphor-containing medicinal products are single substance formulations. Most products contain more than one active substance and present a wide range of different combinations, which include other terpenes such as menthol, eucalyptol and turpentine oil.

Outcome of the assessment

Camphor has a cyclic terpene structure that makes it highly lipophilic, explaining its large volume of distribution, rapid movement across mucous membranes and, possibly, an attraction to myelinated axons, which could explain the neurological adverse events. However, the pharmacologic activity of camphor after oral ingestion is not well studied. The fatal dose is considered as 50-500mg/kg, or for a one year-old child, 400mg.

The PhVWP therefore concluded that the summaries of product characteristics (SmPCs) and package leaflets (PLs) for medicinal products for topical or inhaled use containing 400 mg or more camphor in a single package should be amended to improve the information on the symptoms and management of overdose following accidental intake.

Symptoms include gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea, abdominal pain) as well as neurological symptoms (e.g. headache, vertigo, feeling hot/flushing, convulsions, respiratory depression and coma).

These symptoms should be treated symptomatically. Vomiting should not be induced because of associated risks, such as subsequent inhalation of camphor, with the risk of triggering potentially fatal laryngospasm in small children.

Annex 2

Summary Assessment Report of the PhVWP July 2010

Isotretinoin for oral use – Risk of erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis

Key message

Patients should stop isotretinoin if a serious skin rash develops and see their physician immediately, as this could mark the onset of a potentially life-threatening skin reaction (i.e. erythema multiforme, Stevens Johnson syndrome or toxic epidermal necrolysis).

Safety concern and reason for current safety review

In March 2010, the PhVWP reviewed three types of severe skin reaction. Based on the available evidence, the PhVWP recommended that the risk of erythema multiforme should be added to the summaries 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 the remaining two types of skin reaction, namely Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis, the PhVWP in March 2010 considered that the available evidence did not support their addition to the product information (see PhVWP Monthly Report March 2010).

Since then a further case of SJS has occurred and this has resulted in a new review of these types of severe skin reaction.

Clinical setting

Isotretinoin is indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical treatment.

Information on the data assessed

The PhVWP reviewed the available data and heard an Oral Clarification from the marketing authorisation holder for the originator product.

Outcome of the assessment

Based on the available data, the PhVWP concluded that a causal association between isotretinoin and the reactions Stevens Johnson syndrome and toxic epidermal necrolysis cannot be excluded and that these skin reactions should also be included in the SmPCs and PLs of oral isotretinoin-containing products, in addition to erythema multiforme.

The SmPC and PL should contain the information that these potentially life-threatening reactions may be difficult to distinguish from other skin reactions, describe to the patient their signs and symptoms and advise to stop isotretinoin and see the physician immediately if serious skin rash develops.