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Pharmacovigilance Working Party (PhVWP)

February 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its February 2011 plenary meeting on 14-16 February 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, go to: about us/Committees/CHMP/Committees meeting reports).

Montelukast – Reports of psychiatric and behaviour-related adverse reactions

Psychiatric and behaviour-related adverse reactions have been reported in patients treated with montelukast. The PhVWP review concludes that this information is adequately reflected in the existing EU product information. Risk management plans on the use of montelukast in children have been initiated.

Triggered by the assessment of the latest periodic safety update report (PSUR) for montelukast and a safety update issued by the US Food and Drug Administration (FDA) in August 2009, the PhVWP initiated a review to determine if the current EU product information for montelukast adequately describes the reports of psychiatric adverse events or if there is a need for strengthened wording.

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Based on the review, the PhVWP concluded that the available data do not warrant additional information in the existing EU product information regarding psychiatric and behaviour-related adverse reactions. However it was noted that in some countries there was a greater than expected reporting of psychiatric reactions in children. The emerging data will continue to be closely monitored. As an additional measure, the PhVWP asked that the originator marketing authorisation holder submits a risk management plan (RMP) in order to gather further information on the use of montelukast in children and observed adverse reactions in this specific patient group. RMPs for generic products may be requested at a later stage as appropriate following assessment of the RMP for the originator product. Montelukast is a leukotriene receptor antagonist authorised for the oral treatment of asthma and allergic rhinitis (see Annex 1 for the Summary Assessment Report).

Paracetamol – Available evidence does not support a causal relationship between paracetamol and asthma in children after exposure in pregnancy or use in early infancy

As with other medicines, paracetamol should only be used during pregnancy or in children if clearly necessary.

Given recent studies, the PhVWP reviewed the possible causal association between paracetamol and asthma in children after exposure in pregnancy or use in early infancy and concluded that the available data do not establish causality. Considering the uncertainties surrounding the current evidence, no regulatory action is considered necessary. Any newly emerging data will be carefully reviewed.

As with other medicines, paracetamol should only be used during pregnancy or in children if clearly necessary (see Annex 2 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.

European Medicines Agency's Transatlantic Workshop on Drug-Related Progressive Multifocal Leukoencephalopathy

The PhVWP welcomed confirmation that the European Medicines Agency will host this workshop, co-chaired with the US Food and Drug Administration (FDA), on 25-26 July 2011. The objectives of this workshop are to find common understanding on ongoing research and future research priorities, to foster approaches to research funding and partnerships and to agree on mechanisms to ensure information-sharing and regular stock take of existing and missing knowledge in relation to drug-related progressive multifocal leukoencephalopathy (PML) (Interested readers are referred to http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/02/event_detail_000399.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c3).

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 February 2011

Montelukast – Reports of psychiatric and behaviour-related adverse reactions

Key message

Psychiatric and behaviour-related adverse reactions have been reported in patients treated with montelukast. The PhVWP review concludes that this information is adequately reflected in the existing EU product information. Risk management plans on the use of montelukast in children have been initiated.

Safety concern and reason for current safety review

The assessment of the periodic safety update report (PSUR) for montelukast, covering the period from 31 July 2006 to 30 July 2009, led to the conclusion that the reports received through spontaneous reporting on psychiatric and behaviour-related adverse events required further evaluation.

Also, the US Food and Drug Administration (FDA) published the outcome of their safety review in August 2009, together with their request to marketing authorisation holders to update the product information in the US with the advice that patients should be instructed to notify their healthcare professionals if neuropsychiatric changes occur and that in such cases, healthcare professionals should carefully evaluate the risks and benefits of continuing treatment with montelukast [1].

The PhVWP therefore initiated a review to determine if the current EU product information for montelukast adequately describes the reports of psychiatric adverse events or if there is a need for strengthened wording.

Clinical setting

Montelukast is a selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene type-1 (CysLT1) receptor. It is authorised for the oral treatment of asthma and allergic rhinitis.

Information on the data assessed

The data assessed included data from the periodic safety update reports (the last six PSURs for the originator product and eleven PSURs for generic products) and additional data requested from the originator marketing authorisation holder, supplemented by searches for adverse reaction reports in the EudraVigilance and the VigiBase[1] databases.

The additional data requested from the originator marketing authorisation holder included data from pooled analyses of clinical trial data, a detailed cumulative analysis of psychiatric adverse events reported in the post-authorisation phase, background incidences, separate analyses looking at reporting rates in children versus adults and by different geographical areas, a disproportionality analysis from their adverse reaction database and data from the medical literature on the effects of leukotrienes or montelukast on the central nervous system, in particular on possible mechanisms.

[1] VigiBase is the database for worldwide adverse reaction reports maintained by the WHO Collaborating Centre for International Drug Monitoring.

Outcome of the assessment

Based on the review, the PhVWP concluded that the available data do not warrant additional information in the product information for montelukast in the EU regarding case reports of psychiatric and behaviour-related adverse reactions, however it was noted that in some countries there was a greater than expected reporting of psychiatric reactions in children.

The current core safety profile (CSP) agreed between the competent authorities of Member States in the framework of the work sharing procedure for the assessment of PSURs already includes that psychiatric disorders have been reported, specifying the following reactions: dream abnormalities (including nightmares), hallucinations, insomnia, irritability, anxiety, restlessness, agitation (including aggressive behaviour), tremor, depression, suicidal thinking and behaviour (suicidality).

The emerging data will continue to be closely monitored. As an additional measure, the PhVWP asked that the originator marketing authorisation holder submits a risk management plan (RMP) in order to gather further information on the use of montelukast in children and observed adverse reactions in this specific patient group. RMPs for generic products may be requested at a later stage as appropriate following assessment of the RMP for the originator product.

References

[1] Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast (marketed as Accolate), and zileuton (marketed as Zyflo and Zyflo CR). Silverspring, MD: US Food and Drug Administration; 29 Aug 2009. Available under http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm (last accessed on 17 Feb 2011).

Annex 2

Summary Assessment Report of the PhVWP February 2011

Paracetamol – Available evidence does not support a causal relationship between paracetamol and asthma in children after exposure in pregnancy or use in early infancy

Key message

The available evidence does not support a causal relationship between paracetamol and asthma in children after exposure in pregnancy or use in early infancy. As with other medicines, paracetamol should only be used during pregnancy or in children if clearly necessary.

Safety concern and reason for current safety review

A possible causal association between paracetamol and asthma after exposure in pregnancy or use in early infancy was first suggested from ecological studies and various biological mechanisms to explain this association have been proposed. Over the last ten years an increasing number of epidemiological studies investigating this issue have been conducted.

The possible causal association between paracetamol and asthma after exposure in pregnancy or use in early infancy was last considered by the PhVWP in 2008, and since then a number of epidemiological studies investigating this possibility have been published [1-9]. Therefore, the PhVWP initiated a review of the results of these studies.

Clinical setting

Paracetamol, due to its safety profile, is generally considered the analgesic of choice in both pregnancy and childhood.

Information on the data assessed

To date most of the studies conducted to investigate the possible causal association between paracetamol and asthma after exposure in pregnancy or use in early infancy have been cross-sectional surveys which have had limitations in their design. More recent studies [1-9] on the possible causal association between paracetamol and asthma in children after exposure in pregnancy or use in early infancy include birth cohort studies. These have reported conflicting results about whether or not there is a causal association. Evaluation of these studies has highlighted the difficulties surrounding this issue due to possible confounding by indication, as paracetamol is commonly used to treat symptoms of febrile illness/respiratory infections, which may be associated with an increased risk of asthma.

Outcome of the assessment

The PhVWP concluded that a causal relationship between paracetamol and asthma in children after exposure in pregnancy or use in early infancy has not been established from the studies available to date [1-9]. PhVWP noted the lack of therapeutic alternatives to paracetamol for use during pregnancy and in children. Considering the uncertainties surrounding the current evidence, no regulatory action is considered necessary. Any newly emerging data will be carefully reviewed. As with other medicines, paracetamol should only be used during pregnancy or in children if clearly necessary.

References

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