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Patient Health Protection

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Pharmacovigilance Working Party (PhVWP)

December 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its December 2010 plenary meeting on 13-15 December 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/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000190.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028d2a).

Fluoroquinolones – Risk of QT interval prolongation

Product information for fluoroquinolones will include updated advice for avoiding QT interval prolongation.

The PhVWP revised their recommendations of 2003 for the product information of selected fluoroquinolone antibiotics[1] with regard to the risk of QT interval prolongation in the light of updated evidence with a view to implementing harmonised product information across Member States of the EU. The PhVWP categorised the fluoroquinolones into three risk categories (potential/low potential/very low potential or insufficient data to assess their potential). For those active substances for which there are currently insufficient data, the PhVWP recommended to the competent authorities in Member

[1] The active substances included in this review were enoxacin, gemifloxacin (EU marketing authorisation application withdrawn), levofloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin.

European Medicines Agency
7 Westferry Circus ● Canary Wharf
London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
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 1 634 3453 **Facsimile** +353 1 661 4764
E-mail hma-ps@imb.ie **Website** www.hma.eu

States to encourage marketing authorisation holders to carry out appropriate studies (see Annex 1 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.

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.

Work plan for the CHMP Pharmacovigilance Working Party 2011

The PhVWP noted that the CHMP adopted the PhVWP work plan 2011 submitted by the PhVWP in November 2010. In 2011, the PhVWP will focus on the implementation of the new legislation (see PhVWP Monthly Report 1009), in addition to their continuous safety monitoring of medicines. For the work plan, interested readers are referred to the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000019.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028d92).

Meetings of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in November 2010

The PhVWP welcomed the outcome of the latest ICH meetings, where a pharmacovigilance brainstorming session was held on safety update reporting, as well as, on approaches for benefit-risk evaluation and current legislative parameters and regional constraints. During the session a shared vision of pharmacovigilance aiming at optimised lifecycle benefit-risk evaluation of medicines for promoting public health was developed and subsequently the ICH Steering Committee endorsed the establishment of a new ICH Working Group on periodic benefit-risk evaluation reporting[2]. The PhVWP will contribute to the continuation of this work within the ICH framework.

[2] See ICH website http://www.ich.org/ichnews/newsroom/read/article/new-ich-guideline-set-to-replace-current-e2c-guideline.html.

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 December 2010

Fluoroquinolones – Risk of QT interval prolongation

Key message

Product information for fluoroquinolones will include updated advice for avoiding QT interval prolongation.

Reason for current safety review

The PhVWP carried out a review of fluoroquinolones with regard to the risk of QT interval prolongation, triggered by discrepancies noted for some products between the current summaries of product characteristics (SmPCs) and the recommendations agreed by the PhVWP in April 2003 in relation to this risk for the SmPC section 4.4 on warnings and precautions of use.

The active substances included in this review were enoxacin, gemifloxacin (EU marketing authorisation application withdrawn), levofloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin.

Safety concern

QT interval prolongation is an irregularity of the electrical activity of the heart that places patients at risk of ventricular arrhythmias. The identification of patients at risk of QT interval prolongation induced by a medicine may help to prevent these events.

Clinical setting

Fluoroquinolones are broad-spectrum antibacterial agents.

Information on the data assessed

The PhVWP reviewed, for each substance, all available data and information from non-clinical and clinical studies as well as data from post-authorisation studies and spontaneous reporting covering the period from 1 December 1999 to 31 December 2008.

Outcome of the assessment

The PhVWP concluded that, with respect to the potential for inducing QT interval prolongation, fluoroquinolones can be divided into three groups based on clinical data and results from *in vivo* studies and *in vitro* electrophysiological studies:

1. Fluoroquinolones with a potential for inducing QT interval prolongation;

   The active substances classified in this group are gemifloxacin and moxifloxacin.

2. Fluoroquinolones with a low potential for inducing QT interval prolongation; and

   The active substances classified in this group are levofloxacin, norfloxacin and ofloxacin.

3. Fluoroquinolones with a very low potential for inducing QT interval prolongation or for which there are insufficient data available to assess their potential completely due to the lack of *in vitro* electrophysiological studies.

   The active substances classified in this group are enoxacin, pefloxacin, prulifloxacin and rufloxacin.

The PhVWP also noted that some fluoroquinolones (especially those in group 1) have the potential for inducing life-threatening torsades de pointes, especially under conditions favouring the development of QT interval prolongation (hypokalaemia, hypomagnesaemia, bradycardia, congenital or acquired prolongation of the QT interval).

Therefore, the PhVWP recommended revising the SmPCs and package leaflets (PL) as follows:

1. For substances with a potential for QT interval prolongation, contraindications in patients with certain risk factors and co-medications should be included in SmPC section 4.3 (and section 4.5 on interactions), detailed advice on precautions should be provided in section 4.4, and section 4.8 should include QT interval prolongation, ventricular tachyarrhythmia, syncope, torsade de pointes and cardiac arrest as adverse reactions. Advice on stopping treatment and performing electrocardiography (ECG) if signs of cardiac arrhythmia occur during treatment should be provided in section 4.4, as well as treatment advice of overdose in section 4.9.

   The PL should list the contraindications, contra-indicated co-medications and adverse reactions, provide advice on other risk factors and ask patients to inform their physicians before taking the medicine if they have a history of abnormal heart rhythm or are taking medicines lowering potassium blood levels and to contact their physician immediately if they experience irregular heart beats.

2. For substances with a low potential for QT interval prolongation, advice on cautious use should be provided in SmPC section 4.4 and advice on interactions with other medicines known to prolong the QT interval in section 4.5. Section 4.8 should include ventricular arrhythmia, torsade de pointes and prolongation of ECG QT interval as adverse reactions, and advice on treatment of overdose should be provided in section 4.9.

   The PL should list the adverse reactions, provide advice on risk factors and ask patients to inform their physicians before taking the medicine if they have a history of abnormal heart rhythm or are taking other QT interval prolonging medicines.

3. For substances with a very low potential for QT interval prolongation or for which there are insufficient data available to assess their potential completely, the potential should be mentioned in SmPC section 4.4, and section 4.8 on adverse reactions should be completed reflecting the cases reported for the respective substance.

   The PL should list the reported adverse reactions and ask patients to inform their physicians before taking the medicine if they have a history of abnormal heart rhythm.

For those active substances for which there are currently insufficient data (i.e. enoxacin, pefloxacin and rufloxacin), the PhVWP recommended to the competent authorities in Member States to encourage marketing authorisation holders to carry out appropriate studies.