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Pharmacovigilance Working Party (PhVWP)

May 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its May 2010 plenary meeting on 17-19 May 2010.

Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy (see http://www.ema.europa.eu/htms/human/phv/reports.htm). The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States.

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 (see http://www.ema.europa.eu/pressoffice/presshome.htm).

Low-molecular-weight iron dextran – Risk of allergic reactions

Risk of serious allergic reactions due to parenteral administration of low-molecular-weight iron dextran requires appropriate precautionary measures

The PhVWP investigated the risk of serious allergic reactions following the parenteral administration of low-molecular-weight (LMW) iron dextran, following data from spontaneous reporting in France.

The review revealed that the worldwide reporting rate of serious allergic reactions for LMW iron dextran is 0.009 reported cases/1000 DDDs[1] while it is 0.1 reported cases/1000 DDDs in France. Given the low worldwide reporting rate, the PhVWP concluded that no regulatory action is necessary at present apart from the risk minimisation measures that the French competent authority has decided to put in place. These measures aim to raise awareness of the risk and the need for appropriate precautionary measures (test dosing and patient monitoring), and to monitor the use of LMW iron

[1] [1] Defined Daily Doses as defined by the WHO Collaborating Centre for Drug Statistics Methodology.

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dextran and associated allergic reactions in France. The impact of the measures will be assessed in France in one year (see Annex 1 for the Summary Assessment Report).

Rosuvastatin – Risk of diabetes

Risk of developing diabetes slightly increased in pre-diabetic patients (fasting glucose plasma levels of 5.6 - 6.9 mmol/l) due to use of rosuvastatin

The PhVWP performed a review of the risk of developing diabetes mellitus with rosuvastatin. This safety concern arose from findings from the JUPITER clinical trial[2]. The PhVWP concluded that a statement should be added to the warning section of the summary of product characteristics (SmPC) for rosuvastatin, stating that the risk of diabetes mellitus is slightly increased in pre-diabetic patients (fasting glucose plasma levels of 5.6 - 6.9 mmol/l), together with a reference to the adverse reaction section of the SmPC.

Considering the risk of diabetes mellitus in light of the benefits of treatment with rosuvastatin, the PhVWP concluded that the benefits of rosuvastatin continue to outweigh the risk of diabetes mellitus and that the overall benefit-risk balance of rosuvastatin remains positive. Rosuvastatin is an HMG-CoA reductase inhibitor (the class of medicines commonly known as statins) used in patients with elevated blood lipid levels (primary hypercholesterolaemia or mixed dyslipidaemia and homozygous familial hypercholesterolaemia).

This review was performed as part of the assessment of an application for a variation to a marketing authorisation in the framework of a mutual recognition procedure. Therefore, the CMD(h) has been informed of the conclusion of the PhVWP. The variation assessment report will be made available to the public on the HMA website (http://www.hma.eu/index.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 – Period Safety Update Report

RMP – Risk Management Plan

SmPC – Summary of Product Characteristics

[2] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; 359: 2195-2207.

Annex 1

Summary Assessment Report of the PhVWP May 2010

Low-molecular-weight iron dextran – Risk of allergic reactions

Key message

Risk of serious allergic reactions due to parenteral administration of low-molecular-weight iron dextran requires appropriate precautionary measures.

Safety concern and reason for current safety review

Recently, the reporting rate of spontaneous case reports of serious allergic reactions in France following administration of the low-molecular-weight (LMW) iron dextran-containing product FERRISAT (named COSMOFER in some other Member States) was found to be unexpectedly higher than that reported with other iron formulations for parenteral use, in particular those containing iron sucrose.

This gave rise to the concern that the risk of serious allergic reactions following administration of LMW iron dextran might exceed the risk of other iron formulations for parenteral use.

Therefore, the PhVWP considered it necessary to investigate the frequency and characteristics of allergic adverse reactions observed in association with the administration of LMW iron dextran.

Clinical setting

Parenteral administration of iron compounds is indicated when oral dosage forms are either not tolerated or are inefficient, such as when there is a need to restore iron reserves rapidly.

Information on the data assessed

A list of questions was forwarded to the marketing authorisation holder for FERRISAT in March 2010, requesting its updated views on the overall safety profile of LMW iron dextran and on the French data as well as requesting a review of the scientific literature. The responses from the marketing authorisation holder were based on the cumulative worldwide data from the periodic safety update reports (PSURs) and on the data collected through the review of the literature [1-13].

The review of the PSURs covering the period 24 February 2004 – 31 March 2010 confirmed that the spontaneous reporting rate of serious allergic reactions requiring anti-allergy medication is low: a total of 328 case reports of allergic reactions were received through spontaneous reporting, and the use of the medicine during this period was estimated to be 12.75 million DDDs (1 DDD = 100 mg)[3]. Among the reported cases, the use of anti-allergy medication (parenteral adrenaline, corticosteroids or antihistamines) was reported in 111 cases. Because of the need for medication, these 111 cases were considered to be serious allergic reactions, resulting in a reporting rate of 0.009 reported cases/1000 DDDs.

In comparison, the reporting rate in France since the launch of LMW iron dextran in March 2008 was calculated to be 0.1 reported cases/1000 DDDs (37 serious allergic reactions reported with 155.551

[3] Defined Daily Doses as defined by the WHO Collaborating Centre for Drug Statistics Methodology.

DDDs). The use of the product in France since the launch in that country in 2008 accounts for only around 1% of the cumulative worldwide use since first launch in 2001.

The literature review confirmed the low worldwide reporting rate of serious allergic reactions for LMW iron dextran. Spontaneous reporting data indicated that the reporting rate of serious allergic reactions for iron sucrose may be slightly lower than for LMW iron dextran. However, direct head-to-head comparisons between different parenteral iron compounds are neither available nor considered feasible to carry out.

Outcome of the assessment

The PhVWP agreed to closely monitor the effects of the risk minimisation measures that the French competent authority decided to put in place in France. These risk minimisation measures include a Direct Health Care Professional Communication raising awareness of the risk of serious allergic reactions due to parenteral administration of LMW iron dextran and the need for appropriate precautionary measures (test dosing and patient monitoring). In addition, they include a drug utilisation study and a plan for the re-assessment of the situation in France in one year. The PhVWP concluded that no further regulatory action is necessary at present.

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