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Pharmacovigilance Working Party (PhVWP)

April 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its April 2010 plenary meeting on 19-20 April 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). Any position agreed by the PhVWP for non-centrally authorised products forms a recommendation 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 on its request. For safety updates concerning these products, readers are referred to the CHMP Monthly Report (see http://www.ema.europa.eu/pressoffice/presshome.htm).

Dipyridamole in combination with acetylsalicylic acid – No evidence for increased risk of ischaemic stroke versus acetylsalicylic acid alone in the European population

Results from the JASAP trial conducted in Japan do not change the positive benefit-risk balance of dipyridamole in combination with acetylsalicylic acid for the European population

The PhVWP reviewed the results of the JASAP clinical trial conducted in Japan and of previous studies conducted in Europe in relation to the incidence of recurrent ischaemic stroke. The increased incidence of recurrent ischaemic stroke seen in the subpopulations of diabetic and hypercholesterolaemic patients of the Japanese trial population taking dipyridamole in combination with acetylsalicylic acid (ASA) in comparison to ASA alone were not identified in the same subpopulations of patients taking part in the European studies. The PhVWP therefore concluded that the results from the JASAP trial do not change the positive benefit-risk balance of dipyridamole in combination with ASA for the non-Japanese population and hence the results were not considered entirely applicable to the population in

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Europe. Changes to the product information in the EU were not deemed necessary (see Annex 1 for the Summary Assessment Report).

Latanoprost – No evidence for risk of malignant melanomas of the eye and skin

Causal relationship between latanoprost and malignant melanomas of the eye and skin not supported by available data

The PhVWP performed an assessment of the possible causal relationship between latanoprost and the risk of malignant ocular and cutaneous melanomas. The PhVWP concluded that the concern over a possible causal relationship was not supported by the available data and that no regulatory action was needed. This issue will be kept under close monitoring and any relevant data which may arise in the future will be carefully evaluated (see Annex 2 for the Summary Assessment Report).

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 April 2010

Dipyridamole in combination with acetylsalicylic acid – No evidence for increased risk of ischaemic stroke versus acetylsalicylic acid alone in the European population

Key message

Results from the JASAP trial conducted in Japan do not change the positive benefit-risk balance of dipyridamole in combination with acetylsalicylic acid for the European population.

Safety concern and reason for current safety review

A clinical trial was conducted in Japan to show the non-inferiority of the product AGGRENOX (fixed combination of sustained-release dipyridamole 200 mg and acetylsalicylic acid 25 mg to be taken twice a day) to acetylsalicylic acid (ASA) 81 mg once a day over 52 weeks in preventing recurrent ischaemic stroke (i.e. stroke caused by failure of the blood supply to part of the brain, also called cerebral infarction). This trial, called JASAP for Japanese Aggrenox Stroke Prevention vs. Aspirin Programme, was a randomised, double-blind, active-controlled, double-dummy trial in 1,295 patients in Japan [1].

The marketing authorisation holder for AGGRENOX, which holds authorisations in some Member States under various invented product names, reported the results from the JASAP trial to the competent authorities in Member States. The results showed a significant increase in the incidence of recurrent ischaemic stroke in patients with diabetes or hypercholesterolaemia when using dipyridamole in combination with ASA compared with ASA alone.

Therefore, the PhVWP performed an assessment of the data from this and other available studies.

Clinical setting

Dipyridamole and acetylsalicylic acid (ASA) are both so-called anti-platelet substances that prevent ischaemic stroke by preventing aggregation of thrombocytes (platelets) in the blood. The current internationally recognised guideline for prevention of recurrent ischaemic stroke [2] does not recommend any particular anti-platelet agent(s) for the sub-populations of diabetic or hypercholesterolaemic patients.

Information on the data assessed

The JASAP trial did not meet its primary study objective to show non-inferiority of AGGRENOX to ASA and the incidence of recurrent ischaemic stroke was numerically higher in the AGGRENOX group (6.9%) compared with the ASA group (5.0%) with a hazard ratio of 1.47 (95% CI 0.93, 2.31). The upper limit of the 95% CI and even the point-estimate exceeded the protocol-specified non-inferiority margin of 1.37.

Additional analyses on bleeding events and hazard ratios for all stroke events (composite endpoint of cerebral infarction, cerebral or subarachnoid haemorrhage) in the JASAP trial showed a higher risk of all stroke and ischaemic stroke in the diabetes and the hyperlipidaemic subgroups treated with

AGGRENOX compared to ASA. In the hyperlipidaemic subgroup the risks of haemorrhagic stroke, major bleed and intracerebral haemorrhage were increased too.

No plausible mechanism has been found to explain these results. Overall, the results of the JASAP trial were inconclusive regarding the benefit-risk balance of dipyridamole in combination with ASA in the Japanese population.

Efficacy and safety data on diabetic and hypercholesterolaemic subgroups from studies previously conducted in Europe (ESPS-2 study and PRoFESS study) showed no significantly increased risk of recurrent ischaemic stroke.

Outcome of the assessment

The PhVWP considered the results of the JASAP trial and of studies conducted in Europe. In the European studies no increased risk of recurrent ischaemic stroke in the diabetic and hypercholesterolaemic subpopulations has been identified for dipyridamole in combination with ASA in comparison with ASA alone. The PhVWP therefore concluded that there is an unexplained higher risk in the diabetic and hypercholesterolaemic Japanese subpopulations which does not change the positive benefit-risk balance of dipyridamole in combination with ASA for the non-Japanese population and hence the results were not considered entirely applicable to the population in Europe. Changes to the product information in the EU were not deemed necessary.

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Annex 2

Summary Assessment Report of the PhVWP April 2010

Latanoprost – No evidence for risk of malignant melanomas of the eye and skin

Key message

Causal relationship between latanoprost and malignant melanomas of the eye and skin not supported by available data.

Safety concern and reason for current safety review

A concern arose from spontaneously reported cases and data from the scientific literature suggesting a possible causal relationship between latanoprost and malignant ocular and cutaneous melanomas.

Latanoprost has been shown to increase iris pigmentation [5] and it has been hypothesised that this may be due to either increased synthesis of melanin (melanogenesis) or to an increase in proliferation of melanocytes in the eye [7]. The latter possible mechanism gave rise to the hypothesis of a potential carcinogenic effect of the active substance.

Malignant melanomas, including those of the eye and skin, are forms of cancer which are rare but serious and potentially fatal. Age, light pigmentation and exposure to ultraviolet light are independent risk factors for these two melanoma types.

Clinical setting

Latanoprost is a prostaglandin F2α analogue that is used to reduce the pressure inside the eye in patients with open angle glaucoma or ocular hypertension. If untreated, such increased intraocular pressure (IOP) may lead to progressive and irreversible vision loss.

Information on the data assessed

Given the concern, the marketing authorisation holder was requested to submit a cumulative review of all the data from preclinical trials, clinical trials, spontaneous reporting and other information. Based on this review and data from the scientific literature [1-31], the PhVWP performed an assessment of the possible causal relationship between latanoprost and the risk of malignant melanomas.

Outcome of the assessment

The PhVWP considered that the hypothesis for development of malignant ocular and cutaneous melanomas due to latanoprost-induced melanocyte proliferation (which is apparent by hyperpigmentation) was not supported by the available data from in vitro or in vivo studies.

Given the extensive use of latanoprost, the number of cases of malignant melanoma from spontaneous reporting is relatively small to date (15 cases of ocular and 6 of cutaneous melanoma during an estimated exposure of 26 million patient-years). In addition, the patients with malignant melanomas were of advanced age, which is an independent risk factor for both melanoma types.

However, it was recognised that stimulation of the production of melanin within individual melanocyte cells has been shown with latanoprost and warnings about increased skin pigmentation are already included in the product information.

In light of the small number of cases, the advanced age of the patients and the lack of supportive data from in vitro and in vivo studies it was considered that the available data did not support a causal relationship. Therefore, the PhVWP concluded that no regulatory action was needed but the issue will be kept under close monitoring and any relevant data which may arise in the future would be carefully evaluated.

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