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Patient Health Protection

Monthly report

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Pharmacovigilance Working Party (PhVWP)

November 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its November 2010 plenary meeting on 15-17 November 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.

Corticosteroids for inhalational or intranasal use – Risk of psychiatric, behavioural and other systemic adverse reactions

Systemic adverse reactions may occur with inhaled and intranasal corticosteroids, including psychiatric and behavioural reactions. Growth should also be monitored in children using intranasal or inhaled corticosteroids.

The PhVWP reviewed the risk of systemic adverse reactions associated with corticosteroids for inhalational or intranasal use¹. The PhVWP concluded that – given the reported cases, coupled with biological plausibility and the knowledge on adverse psychiatric and behavioural reactions to corticosteroids administered systemically (i.e. orally or by injection) – harmonised key elements should

¹ The active substances included in this review were beclometasone, betamethasone, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone, mometasone, prednisolone, tixocortol and triamcinolone.

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be added to the existing summaries of product characteristics (SmPCs) and package leaflets (PLs) across all corticosteroids for each formulation (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For practical information on implementation interested readers are advised to consult the HMA website <http://www.hma.eu/cmdh.html>.

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 Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

The PhVWP welcomed the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, issued by the Agency for public consultation on 8 November 2010 and provided their comments (for the guide under public consultation see http://www.encepp.eu/public_consultation/index.html).

In addition, the PhVWP noted the public ENCePP Information Day scheduled for 26 November 2010 (for more information see http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2010/07/event_detail_000325.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c31).

Research on Direct Healthcare Professional Communications (DHPCs) in the Netherlands

The PhVWP heard results from research on Direct Healthcare Professional Communications (DHPCs) undertaken by the University Medical Center Groningen in collaboration with the Dutch Medicines Evaluation Board². The PhVWP welcomed this research, as well as the interim results from further research, as a contribution to future improvement of communication on the safe use of medicines.

² Mol, PGM, Straus SMJM, Piening S, et al. A decade of safety-related regulatory action in the Netherlands: a retrospective analysis of direct healthcare professional communications from 1999 to 2009. *Drug Safety*. 2010, 33: 463-474.

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 November 2010

Corticosteroids for inhalational or intranasal use – Risk of psychiatric, behavioural and other systemic adverse reactions

Key message

Systemic adverse reactions may occur with inhaled and intranasal corticosteroids, including psychiatric and behavioural reactions. Growth should also be monitored in children using intranasal or inhaled corticosteroids.

Reason for current safety review

The competent authority in the United Kingdom reviewed the evidence for the risk of adverse psychiatric and behavioural reactions with systemic use (i.e. oral intake or injection) of corticosteroids. This review suggested that the product information for corticosteroids administered by inhalational or intranasal routes should contain a more detailed description of the risk of adverse psychiatric and behavioural reactions.

Therefore, the PhVWP undertook a review of adverse psychiatric and behavioural reactions associated with the use of corticosteroids for inhalational or intranasal use and of systemic adverse reactions associated with corticosteroids for intranasal use. The active substances included in this review were beclometasone, betamethasone, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone, mometasone, prednisolone, tixocortol and triamcinolone.

Safety concern

It is widely known that the systemic use of corticosteroids is associated with the rare occurrence of adverse psychiatric and behavioural reactions. It is therefore plausible to presume that the same effects may be seen with any corticosteroid which may exert systemic effects, such as inhaled and intranasal corticosteroids, albeit far less frequently than with systemic formulations. Examples of adverse psychiatric and behavioural reactions include psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression.

In some Member States the risk of adverse psychiatric reactions is already included in the product information for some but not all corticosteroids for inhalation.

Non-psychiatric systemic adverse reactions are also known to occur with inhaled and intranasal corticosteroids. Examples of such reactions include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract and glaucoma.

While non-psychiatric systemic adverse reactions are described in the product information for inhaled corticosteroids, the product information for intranasal corticosteroids includes only a general reference to such risks and specific examples (such as adrenal suppression and ocular effects) are not included.

Systemic in this context means that the medicine may be absorbed into the blood circulation from the site of application and have general rather than only local effects.

Clinical setting

Inhaled corticosteroids are prescription-only medicines, indicated in the prophylactic management of persistent asthma.

Intranasal corticosteroid-containing products are available as prescription-only medicines or in a pharmacy without prescription. Intranasal corticosteroids have a number of indications, including prophylaxis and treatment of seasonal allergic or perennial rhinitis, treatment of nasal polyps and treatment of non-infected inflammatory conditions of the nose.

The medical literature suggests that psychiatric and behavioural disorders are more frequently reported in patients with asthma or allergy. However, it is also the case that treatment with inhaled and intranasal corticosteroids is widespread in these patient groups, as is treatment with substances known to be associated with behavioural and sleep disorders, such as sympathomimetics. A significant proportion of patients show symptoms of both allergic rhinitis and asthma and may therefore be treated simultaneously with inhaled and intranasal steroids, which may increase the risk of adverse reactions.

Information on the data assessed

The data reviewed included cases of suspected adverse psychiatric and behavioural reactions reported for inhaled and intranasal corticosteroids through spontaneous reporting schemes in Member States, published epidemiological studies and other publications [1-6], information on systemic exposure and pharmacokinetics and data on the usage of inhaled and intranasal corticosteroids in the United Kingdom.

Outcome of the assessment

A number of well-documented case reports of adverse psychiatric and behavioural reactions to inhaled and intranasal corticosteroids were noted. There were limitations for some of the spontaneously reported cases which did not allow for conclusions to be drawn on the causal relationship, for example because of the frequent concomitant use of medicines known to be causally associated with behavioural abnormalities. However, several cases appeared not to include alternative possible causes or involved positive re-challenge.

There was little evidence of more severe adverse psychiatric reactions (such as psychosis or suicidal behaviour) associated with inhaled or intranasal corticosteroids.

A disproportionately large number of cases of adverse psychiatric reactions were reported in children compared with adults.

A number of cases of non-psychiatric systemic adverse reactions have been reported spontaneously in the EU or published in the medical literature for intranasal corticosteroids, particularly systemic effects known to be associated with the use of inhaled corticosteroids such as adrenal suppression, growth retardation in children and ocular effects. The number of cases is small in relation to the extensive use of these products, but includes several cases where a reasonable causal association with the use of the intranasal corticosteroids could not be excluded, particularly cases where intranasal steroids were used at high doses or for prolonged periods.

It was noted that intranasal corticosteroids may be associated with a lower risk of systemic adverse reactions than inhaled corticosteroids, due to lower recommended doses, shorter or seasonal duration of treatment and lower systemic absorption and distribution.

Overall, the PhVWP concluded that – given the reported cases, coupled with the biological plausibility of systemic effects and the knowledge of adverse psychiatric reactions to corticosteroids administered systemically – harmonised key elements should be added to the existing product information across all corticosteroids for each formulation. As absorption of inhaled corticosteroids is likely to be higher than that of intranasal corticosteroids and as inhaled corticosteroids are more likely to be used long-term, the PhVWP concluded that it is appropriate to have reduced wording in the product information for intranasal corticosteroids. Based on evidence that some other systemic adverse reactions may also occur with the use of intranasal corticosteroids, the PhVWP further concluded that it is appropriate to include specific examples of these adverse reactions in the product information alongside existing more general warnings.

For the harmonisation of the product information across the EU, the PhVWP recommended that the following key elements be added to the existing information:

For inhaled corticosteroids, the summaries of product characteristics (SmPCs) should contain:

- specific reference to adverse psychiatric reactions, particularly in children, with examples in SmPC sections 4.4 and 4.8.

For intranasal corticosteroids, the SmPCs should contain:

- specific examples of psychiatric and other systemic adverse reactions in SmPC section 4.4, indicating that their likelihood of occurrence is lower than for orally administered corticosteroids;
- information that systemic adverse reactions may occur, particularly at high doses used for long periods in SmPC section 4.8;
- a warning to monitor growth in children in SmPC section 4.4 (if the product is authorised for children);
- information that growth retardation has been reported in children receiving intranasal corticosteroids in SmPC section 4.8 (if the product is authorised for children and supplied as nose drops).

The package leaflets should reflect the amendments to the SmPCs.

References

- [1] Hederes CA. Neuropsychologic changes and inhaled corticosteroids. *J Allergy Clin Immunol.* 2004; 114: 451–452.
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- [3] Stuart FA, Segal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child.* 2005; 90: 500–506.
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- [6] de Vries TW, van Roon EN, Duiverman EJ. Inhaled corticosteroids do not affect behaviour. *Acta Paediatr.* 2008; 97: 786–789.