20 April 2011
EMA/CHMP/PhVWP/298094/2011
Patient Health Protection

Monthly report **Issue number: 1104**

Pharmacovigilance Working Party (PhVWP)

April 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its April 2011 plenary meeting on 11-13 April 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).

BRICANYL TURBOHALER (terbutaline) – Effect of physical impact on accuracy of dose delivery and recommended 100 dose pack size

The PhVWP supported stopping availability of BRICANYL TURBOHALER 0.5 mg/dose containing 200 doses, following assessment of in vitro data demonstrating delivery of excess terbutaline after physical impact to the inhaler, e.g. by dropping. This effect was greater towards the life span end of the 200 dose pack, therefore the PhVWP supported using only a pack size of 100 doses. Patients using a BRICANYL TURBOHALER should, if possible, rinse their mouth after inhalation to minimise systemic uptake of terbutaline into the body.

The PhVWP reviewed data on dose delivery from the inhaler Turbuhaler M2 with regard to accuracy of dose of terbutaline after physical impact to the BRICANYL TURBOHALER (or BRICANYL TURBUHALER in some Member States). Based on these data, the PhVWP considered the potential risk of an increased

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

dose of terbutaline particularly in patients with cardiovascular disease. Although there was evidence of an increase in dose of terbutaline delivered after physical impact to the device e.g. by dropping, particularly at the end of the life span of a 200 dose pack, there was no clinical evidence of a safety concern in use. However, the PhVWP agreed with a proposal to minimise the potential risk by stopping availability of the terbutaline-containing product BRICANYL TURBOHALER 0.5 mg/dose containing 200 doses and using the 100 dose pack only. In addition the PhVWP concluded that the product information of BRICANYL TURBOHALER should be updated with a recommendation that patients should, if possible, rinse their mouth after inhalation to minimise systemic uptake of terbutaline (see Annex 1 for the Summary Assessment Report).

Isotretinoin – Risk of psychiatric reactions

Findings of new epidemiological study by Sundström A et al do not require update of current warnings in the product information for isotretrinoin regarding risk of depression or other psychiatric reactions.

The PhVWP has kept the safety of isotretinoin, a treatment for severe acne, under close review. The PhVWP heard a presentation from Dr A Sundström on his recently published study[1]. This was a study of a large cohort of patients on isotretinoin, comprising 5756 patients on a Swedish registry, followed for 17 197 person-years before, 2905 person-years during and 87 120 person-years after treatment, linked to hospital admissions data. The PhVWP agreed with his interpretation that the study showed an increasing frequency of suicide attempts before treatment with isotretinoin was started and that the study did not provide evidence of an additional risk attributable to isotretinoin on the population level. Given that the product information for isotretinoin-containing medicines includes comprehensive information on the risk of depression associated with isotretinoin and that regular monitoring and close review of any emerging data will continue, the PhVWP further agreed that there was no need to take further regulatory steps on the basis of this study.

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

[1] Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. Br Med J. 2010; 341: c5812.

Annex 1

Summary Assessment Report of the PhVWP April 2011

BRICANYL TURBOHALER (terbutaline) – Effect of physical impact on accuracy of dose delivery and recommended 100 dose pack size

Key message

The PhVWP supported stopping availability of BRICANYL TURBOHALER 0.5 mg/dose containing 200 doses, following assessment of in vitro data demonstrating delivery of excess terbutaline after physical impact to the inhaler, e.g. by dropping. This effect was greater towards the life span end of the 200 dose pack, therefore the PhVWP supported using only a pack size of 100 doses. Patients using a BRICANYL TURBOHALER should if possible rinse their mouth after inhalation to minimise systemic uptake of terbutaline into the body.

Safety concern and reason for current safety review

Inhalers used for the administration of medicines were tested by the Swedish Medicines Product Agency (MPA) with regard to accuracy of dose after physical impact. The inhalers were dropped from a height of 90 cm, as would occur in a fall from a table or kitchen worktop, simulating a situation where the inhaler has been used for some time by a patient (i.e. when a substantial number of doses have been taken). All inhalers withstood the physical impact without apparent mechanical damage. However, the first dose after the fall delivered by the inhaler Turbuhaler M2 was higher than the labelled dose. These increased doses were seen with all medicines administered by means of Turbuhaler M2 and are caused by the design of the mouthpiece necessary to achieve a high proportion of small particles for inhalation. With each delivered dose, a fraction of particles is deposited on the inside of the inhaler, causing an accumulation of the active substance in the inhaler that is proportional to the number of doses taken. With high physical impact, the accumulated substance is set free, causing a considerable increase of the first dose delivered after the fall. Medicinal products using Turbuhaler M2 are BRICANYL TURBOHALER (or BRICANYL TURBUHALER in some Member States) (terbutaline), PULMICORT TURBOHALER (or PULMICORT TURBUHALER in some Member States) (budesonide) and OXIS TURBOHALER (or OXIS TURBUHALER in some Member States) (formoterol).

Given these test results, the concern was raised whether the delivery of an increased dose of these active substances from the Turbuhaler M2 after dropping it at the end of its life span could cause serious adverse reactions.

Therefore, the PhVWP reviewed the test results and other available data.

Clinical setting

Budesonide, formoterol and terbutaline for inhalation are indicated in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Budesonide and formoterol are generally prescribed as maintenance treatment, whereas terbutaline is used on an as-needed basis.

Budesonide is a corticosteroid, while formoterol and terbutaline belong to the medicine class of beta2-agonists.

Information on the data assessed

The data reviewed included the data from the test performed by the MPA and data from similar tests conducted by the marketing authorisation holder for terbutaline and formoterol. Data from clinical trials and post-authorisation studies investigating the safety of high doses of budesonide, formoterol and terbutaline were also reviewed.

Outcome of the assessment

The PhVWP considered that a single high dose of an inhaled corticosteroid, such as budesonide, is not likely to be associated with any serious adverse reaction, and hence was not considered a safety concern.

The PhVWP further considered that beta2-agonists in general are associated with predictable systemic adverse reactions, including those affecting the heart and the cardiovascular system like tachycardia, hypokalaemia, hyperglycaemia and prolongation of the QTc interval. The adverse reactions are dose-dependent and may be aggravated by hypoxia. The clinical significance of these sympathomimetic effects, especially at high doses, has not been adequately established. However, there are case reports, case-control studies, large epidemiological studies and pooled data from randomised placebo-controlled trials reporting an association between the use of beta2-agonists and an increased, dose-dependent risk of myocardial infarction, congestive heart failure, cardiac arrest and sudden cardiac death. Nevertheless, these potential risks should be weighed against the benefit the short-acting beta2-agonist terbutaline can provide for patients with an acute bronchoconstriction. The sympathomimetic effects of long-acting beta2-agonists are less pronounced than those of the short-acting ones, and data from clinical trials studying the tolerability and safety of high doses of formoterol are reassuring.

In the light of the above, the PhVWP considered that the main safety concern with the Turbuhaler M2 after physical impact is the potential risk of cardiovascular reactions following an increased dose of terbutaline in patients with a predisposition for cardiovascular disease. Although there was evidence of an increase in dose of terbutaline delivered after physical impact to the device e.g. by dropping, particularly at the end of the life span of a 200 dose pack, there was no clinical evidence of a safety concern in use. However, the PhVWP agreed with a proposal to minimise the potential risk by stopping availability of the terbutaline-containing product BRICANYL TURBOHALER 0.5 mg/dose containing 200 doses and using the 100 dose pack only. In addition the PhVWP concluded that the product information of BRICANYL TURBOHALER should be updated with a recommendation that patients should, if possible, rinse their mouth after inhalation to minimise systemic uptake of terbutaline.