28 October 2010
EMA/CHMP/PhVWP/652824/2010
Patient Health Protection

Monthly report **Issue number: 1010**

Pharmacovigilance Working Party (PhVWP)

October 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its October 2010 plenary meeting on 18-20 October 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, go to: about us/Committees/Committees meeting reports/CHMP).

Adrenaline-containing auto-injectors EPIPEN/ALTELLUS – Risk of failure of self-injection due to labelling

Patients should check that the arrow on the label of their EPIPEN/ALTELLUS auto-injectors point to the needle (black) end and, if not, consult their pharmacist for advice on replacement.

Following two reports of adverse events (one fatal) possibly associated with the labelling of the auto-injectors, the PhVWP performed an evaluation of the risk of wrongly using the adrenaline-containing auto-injectors named EPIPEN, EPIPEN JR and ALTELLUS. The labelling has now been corrected for the new stock. However, while recall procedures are ongoing and since some of the old products may remain in the possession of patients in some Member States for different periods of time depending on the expiry dates and/or recall procedures, the PhVWP concluded that public communication is warranted in Member States. This communication should include advice for patients to check that the

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

arrow on the label points to the needle end (black end) of the auto-injector and, in if it does not, to consult their pharmacist for advice on replacement (see Annex 1 for the Summary Assessment Report).

Bisphosphonates for oral use – Risk of oesophageal irritation but insufficient evidence to conclude a causal relationship with oesophageal cancer

There is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer. However, bisphosphonate tablets can cause irritation to the oesophagus and therefore patients should follow the instructions in the package leaflet on how to take the medicine and report signs of oesophageal irritation to their physician, such as difficulties or pain on swallowing, chest pain or heartburn. In individual patients with known Barrett's oesphoagus, physicians should carefully consider the benefits and potential risks of treatment with alendronic acid or ibandronic acid.

The PhVWP conducted a review of the risk of oesophageal cancer with oral bisphosphonates[1] following the publication of a study that suggested an increased risk of oesophageal cancer associated with bisphosphonates used orally for the treatment and prevention of certain bone disorders. The PhVWP considered that, given the limitations of this study and a lack of supporting evidence from other studies, there is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer. The PhVWP concluded that the information on the need for a careful benefit-risk consideration in patients with known Barrett's oesophagus (a condition which, in a small number of people, can lead to oesophageal cancer) contained in the summaries of product characteristics (SmPCs) and package leaflets (PLs) for centrally authorised medicinal products containing alendronic acid[2] or ibandronic acid[3] should also be implemented for all nationally authorised alendronic acid-containing medicinal products for oral use. In addition, the PhVWP concluded that, as part of the ongoing monitoring of this risk for all bisphosphonates for oral use, any emerging data on risedronic acid will continue to be evaluated (see Annex 2 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the final wording to be included in the SmPCs and 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.

Long-acting beta$_2$-adrenoceptor agonist bronchodilators formoterol and salmeterol – Review of safety in the management of asthma

The long-acting beta$_2$-adrenoceptor agonist bronchodilators (LABAs) formoterol and salmeterol used in asthma should only be used with an inhaled corticosteroid and doses should be monitored carefully.

The PhVWP conducted an updated review of the safety of the long-acting beta$_2$-adrenoceptor agonist bronchodilators (LABAs) formoterol and salmeterol in the management of asthma. The PhVWP concluded that no regulatory action is warranted in this respect and that the summaries of product characteristics (SmPCs) and package leaflets (PLs) agreed by the PhVWP in 2006 for formoterol- and salmeterol-containing medicinal products appropriately reflect the PhVWP recommendations that LABAs should only be used together with an inhaled corticosteroid (ICS) and that dosing should be monitored

[1] The active substances belonging to the class of bisphosphonates for oral use are alendronic acid, clodronic acid, etidronic acid, ibandronic acid, risedronic acid and tiludronic acid.
[2] Centrally authorised products containing alendronic acid are authorised under the names ADROVANCE, FOSAVANCE and VANTAVO.
[3] Centrally authorised products containing ibandronic acid are authorised under the names BONDENZA, BONVIVA, BONDRONAT and IBANDRONIC ACID TEVA.

carefully. The PhVWP considered that it is important to ensure that the product information is up-to-date in all Member States and agreed key messages for inclusion in any communication to healthcare professionals that may be issued by competent authorities in Member States (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMD(h) accordingly. For the wording to be included in the SmPCs and 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.

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 October 2010

Adrenaline-containing auto-injectors EPIPEN/ALTELLUS – Risk of failure of self-injection due to labelling

Key message

Patients should check that the arrow on the label of their EPIPEN/ALTELLUS auto-injectors point to the needle (black) end and, if not, consult their pharmacist for advice on replacement.

Safety concern and reason for current safety review

The PhVWP performed an evaluation of the risk of wrongly using the adrenaline-containing auto-injectors named EPIPEN, EPIPEN JR or ALTELLUS, following two reports of adverse events (one fatal) possibly associated with the labelling of the auto-injectors.

Clinical setting

EPIPEN, EPIPEN JR and ALTELLUS are available as auto-injectors containing adrenaline for emergency treatment of severe anaphylactic shock or allergic reactions. An auto-injector is a medical device designed for injecting oneself with a specific liquid medicine (usually in an emergency situation).

Information on the data assessed

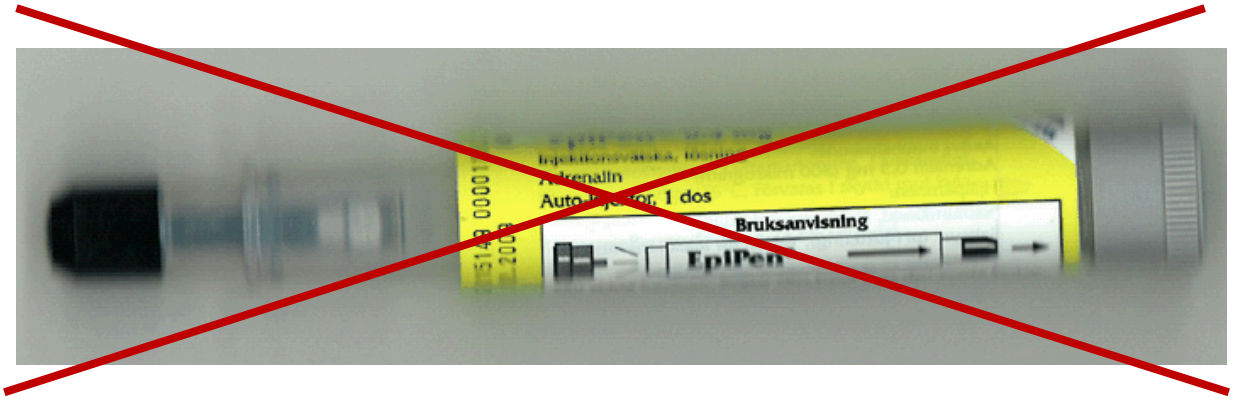
One case of failing to use the auto-injector appropriately occurred in the Czech Republic and resulted in a fatal outcome. There was a further adverse reaction related to the labelling, reported from Norway.

Outcome of the assessment

The PhVWP evaluated the case reports and considered that the auto-injectors, due to reverse direction of the arrow in the diagram on the label, could mislead patients resulting in failure to self-inject (see pictures on next page). Products with this label have been available in 11 Member States of the EU, but the labelling has now been corrected for the new stock. Recall procedures are ongoing and in a short period of time, all products with the old label will have been removed from the EU market.

However, while the recall procedures are ongoing and since some the old products may remain in the possession of patients in some Member States for different periods of time depending on the expiry dates and/or recall procedures, the PhVWP concluded that public communication is warranted in Member States. Such communication should include advice for patients to check that the arrow on the label points to the needle end (black end) of the auto-injector and, if it does not, to consult their pharmacist for advice on replacement.

Wrong label (example of EPIPEN):



Correct label (example of EPIPEN):

Annex 2

Summary Assessment Report of the PhVWP October 2010

Bisphosphonates for oral use – Risk of oesophageal irritation but insufficient evidence to conclude a causal relationship with oesophageal cancer

Key message

There is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer. However, bisphosphonate tablets can cause irritation to the oesophagus and therefore patients should follow the instructions in the package leaflet on how to take the medicine and report signs of oesophageal irritation to their physician, such as difficulties or pain on swallowing, chest pain or heartburn. In individual patients with known Barrett's oesphoagus, physicians should carefully consider the benefits and potential risks of treatment with alendronic acid or ibandronic acid.

Safety concern and reason for current safety review

The PhVWP conducted a review of the risk of cancer of the oesophagus with bisphosphonates tablets following the publication of a study that suggested an increased risk of oesophageal cancer associated with oral bisphosphonates [1].

An increased risk of oesophageal cancer had previously been identified as a potential safety concern with oral bisphosphonates and warnings about the use in patients with Barrett's oesophagus have been added to the product information of the centrally authorised products containing alendronic acid or ibandronic acid and to those originator products containing alendronic acid authorised through the mutual recognition procedure. Barrett's oesophagus is a disease where the cells that line the lower oesophagus have changed because of damage due to acid from the stomach. This disease is a risk factor for oesophageal cancer.

Clinical setting

Bisphosphonates are medicines that are used for the treatment and prevention of bone disorders including hypercalcaemia (high levels of calcium in the blood), for the prevention of bone problems in patients with cancer, and for the treatment of osteoporosis (a disease that makes bones fragile) and Paget's disease (a disease involving bone destruction and re-growth that causes deformity).

The active substances belonging to the class of bisphosphonates for oral use are alendronic acid, clodronic acid, etidronic acid, ibandronic acid, risedronic acid and tiludronic acid.

Oesophageal cancer is cancer of the oesophagus or lower part of the gullet, i.e. the tube that leads from the mouth to the stomach.

Information on the data assessed

The results of the recently published study [1] suggest that there was a small but significant increase in the risk of oesophageal cancer (but not of stomach or colorectal cancers) in individuals who had been prescribed oral bisphosphonates compared with those who had not received bisphosphonates. The incidence rate of oesophageal cancer over 5 years in men and women aged 60–79 years in the general population is 0.5 per 1000 women and 1.5 per 1000 men. In this study, the incidence rate

increased with bisphosphonates use for 5 years to 1 per 1000 women and 3 per 1000 men. Although the study appeared to be well-conducted with a large sample size and long follow-up, it was considered limited in value due to the limited amount of data available in the study database. For example, bisphosphonates are commonly prescribed for women who have sustained fractures. The risk of fractures is associated with smoking and social deprivation, which are also risk factors for oesophageal cancer; however, little information was available in this study for these and other known risk factors for oesophageal cancer, such as consumption of alcohol and previous oesophageal reactions. In addition, patients receiving oral bisphosphonates are more likely to be monitored for oesophageal reactions than those not receiving bisphosphonates. This may result in an increased detection of oesophageal cancer in patients receiving bisphosphonates.

In contrast to the findings of this study [1], an additional study recently published [2] did not find any association between oral bisphosphonates and the risk of oesophageal cancer. However, this study [2] was also limited by the same weaknesses as the previous study [1] in terms of incomplete information in the study database and possibly increased detection of oesophageal cancer in patients receiving bisphosphonates.

Two other studies [3, 4] also did not provide support for a causal relationship.

Outcome of the assessment

The PhVWP considered that, given the limitations in the study [1] and a lack of supporting evidence from other studies [2-4], there is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer.

For alendronic acid, the PhVWP reviewed the existing summaries of product characteristics (SmPCs) and package leaflets (PLs) and concluded that the information regarding Barrett's oesophagus contained in the SmPCs and PLs for centrally authorised medicinal products containing alendronic acid or ibandronic acid and should also be implemented for all nationally authorised alendronic acid-containing medicinal products for oral use. For centrally authorised products, the SmPCs advise physicians to carefully consider the benefits and potential risks of using a bisphosphonate for the individual patient if she/he is known to have Barrett's oesophagus. In the PLs, patients are asked to tell their physician if they have Barrett's oesophagus.

In addition, the PhVWP concluded that the warnings about use in patients with Barrett's oesophagus should not be added to the product information for risedronic acid-containing products; however, as part of the ongoing monitoring of this risk for all bisphosphonates for oral use, any emerging data on risedronic acid will continue to be evaluated.

No other risk minimisation measures or updates to product information were considered necessary by the PhVWP. Any new data that may emerge in the future will be kept under close review.

References

[1] Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. Br Med J. 2010; 341: c4444.

[2] Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. J Am Med Assoc. 2010; 304: 657-663.

[3] Abrahamsen B, Eiken P, Eastell R. More on reports of esophageal cancer with oral bisphosphonate use. N Eng J Med. 2009; 360: 1789.

[4] Solomon DH, Patrick A, Brookhart MA. More on reports of esophageal cancer with oral bisphosphonate use. N Eng J Med. 2009; 360: 1789-1790.

Annex 3

Summary Assessment Report of the PhVWP October 2010

Long-acting beta$_2$-adrenoceptor agonist bronchodilators formoterol and salmeterol – Review of safety in the management of asthma

Key message

The long-acting beta$_2$-adrenoceptor agonist bronchodilators (LABAs) formoterol and salmeterol used in asthma should only be used with an inhaled corticosteroid and doses should be monitored carefully.

Safety concern and reason for current safety review

The safety of the long-acting beta$_2$-adrenoceptor agonist bronchodilators (LABAs) formoterol and salmeterol in the management of asthma was last reviewed in the EU in 2006. At that time, their safety was called into question because the results of two large randomised controlled clinical trials [1, 2] suggested an increased risk of asthma-related events and deaths associated with the use of salmeterol compared with other asthma medication. A published meta-analysis [3] appeared to mirror this finding, and the PhVWP consequently undertook a full review of the safety of LABAs in the management of asthma in children and adults and of chronic obstructive pulmonary disease (COPD).

An updated review has now been carried out by the PhVWP to consider data from a number of important publications which have since become available, to determine whether any further regulatory action is warranted.

Clinical setting

LABAs are prescription-only medicines, indicated in the maintenance therapy of reversible airways obstruction in patients with asthma and chronic obstructive pulmonary disease (COPD). Formoterol has a faster onset of action than salmeterol and for this reason some inhaled products containing formoterol are also indicated in more immediate relief of asthma symptoms.

European and international asthma treatment guidelines recommend the use of LABAs only in patients with moderate to severe asthma as add-on therapy to controller medications such as inhaled corticosteroids (ICS).

Information on the data assessed

The data reviewed included epidemiological data on asthma prevalence [4, 5], meta-analyses published in the medical literature [6, 7], published and unpublished meta-analyses prepared by the US Food and Drug Administration (FDA) [8] and marketing authorisation holders [9], Cochrane reviews [10-15] and observational studies [16-22] as well as data on receptor down-regulation [23-25] and the potential implications of pharmacogenetic findings [26-29].

Outcome of the assessment

On the basis of the review of all the above data, the PhVWP concluded that no new regulatory action is warranted and that the product information agreed by the PhVWP in 2006 for formoterol- and salmeterol-containing medicinal products appropriately reflects their recommendations as follows:

- LABAs should always be prescribed for together with inhaled corticosteroids (ICS) for concomitant use and only when ICS alone is not sufficient to control the asthma symptoms in a patient.
- LABA-ICS combination inhalers should be prescribed when appropriate to aid compliance.
- LABAs should not be prescribed for the relief of exercise-induced asthma symptoms in the absence of regular ICS.
- LABAs should not be initiated in patients with rapidly deteriorating asthma.
- LABAs should be introduced at low dose and the effect properly monitored before considering dose increase; LABAs should be discontinued in the absence of benefit.
- A daily dose of 24 micrograms formoterol should be sufficient for the majority of children, particularly at the younger end of the age range. Higher doses should be used rarely and only when control is not maintained on the lower dose.
- LABA therapy should be reviewed regularly; stepping down therapy should be considered when good long-term asthma control has been achieved.

These recommendations are also consistent with European treatment guidelines.

Furthermore, the PhVWP considered that it is important to ensure that the summaries of product characteristics (SmPCs) and package leaflets (PLs) for formoterol- and salmeterol-containing medicinal products are up-to-date in all Member States. Therefore the PhVWP informed the CMD(h) of this review with a view to completing any outstanding update of product information. In addition, the PhVWP agreed key messages for inclusion in any communication to healthcare professionals that may be issued by competent authorities in Member States.

References

[1] Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. Br Med J. 1993; 306: 1034-1037.

[2] Nelson H, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006; 129: 15-26.

[3] Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med. 2006; 144: 904-912.

[4] Anderson HR, Gupta R, Strachan DP, Limb ES. 50 years of asthma: UK trends from 1955 to 2004. Thorax. 2007; 62: 85-90.

[5] Severe asthma across Europe: a review of available data [report commissioned by Asthma UK]. London: Lung & Asthma Information Society; July 2005.

[6] Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, Yancey S. Metaanalysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med. 2008; 149: 33-42.

[7] Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma: a systematic review. Pulm Pharmacol Ther. 2009; 22: 9-19.

[8] Long-acting beta-agonists and adverse asthma events meta-analysis [statistical briefing package for Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on 10-11 December 2008]. US Food and Drug Administration; 12 Nov 2008.

[9] Benefit risk assessment of salmeterol for the treatment of asthma in adults and children [briefing document for Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on 10-11 December 2008]. Glaxo Smith Kline. Available on the FDA website http://www.fda.gov/ (last accessed on 21 Oct 2010).

[10] Cates CJ, Cates MJ, Lasserson TJ. Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2008; issue 4: CD006923.

[11] Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2008; issue 3: CD006363.

[12] Greenstone IR, Ni Chroinin MN, Masse V, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database Syst Rev. 2005; issue 4: CD005533.

[13] Ni CM, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naïve adults. Cochrane Database Syst Rev. 2005; issue 2; CD005307.

[14] Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev. 2009; issue 3: CD007949.

[15] Walters EH, Gibson PG, Lasserson TJ, Walters JAE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database of Syst Rev. 2007; issue 1: CD001385.

[16] Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. Drug Saf. 2002; 25: 213-223.

[17] Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol. 1996; 49: 247-250.

[18] Perrio MJ, Wilton LV, Shakir SA. A modified prescription-event monitoring study to assess the introduction of Seretide Evohaler in England: an example of studying risk monitoring in pharmacovigilance. Drug Saf. 2007; 30: 681-695.

[19] Sekhsaria S, Alam M, Sait T, et al. Efficacy and safety of inhaled corticosteroids in combination with a long-acting beta2-agonist in asthmatic children under age 5. J Asthma. 2004; 41: 572-582.

[20] Nguyen WT, Stewart C, Fisher K, Tolley E, Lew DB, Self TH. Maintenance asthma treatment with fluticasone propionate/salmeterol combination via Diskus: effect on outcomes in inner-city children enrolled in TennCare. Allergy Asthma Proc. 2005; 26: 129-134.

[21] Stempel DA, Riedel AA, Carranza Rosenzweig JR. Resource utilization with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies in children with asthma. Curr Med Res Opin. 2006; 22: 463-447.

[22] Lyell PJ, Villanueva E, Burton D, Freezer NJ, Bardin Pg. Risk factors for intensive care in children with acute asthma. Respirology. 2005; 10: 436–441.

[23] Fuglsang G, Agertoft L, Vikre-Jorgensen J, et al. Influence of budesonide on the response to inhaled terbutaline in children with mild asthma. Pediatr Allergy Immunol. 1995; 6: 103-108.

[24] Fuglsang G, Vikre-Jorgensen J, Agertoft L, et al. Effect of salmeterol treatment on nitric oxide level in exhaled air dose-response to terbutaline in children with mild asthma. Pedir Pulmonol. 1998; 25: 314-321.

[25] Van Veen A, Weller FR, Wierenga, EA, et al A comparison of salmeterol and formoterol in attenuating airway responses to short-acting β2-agonists. Pulm Pharmacol Ther. 2003; 16: 153-161.

[26] Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the β2-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med. 2000; 162: 75-80.

[27] Green RH, Brightling CE, McKenna S, et al. Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. Eur Respir J. 2006; 27: 1144-1151.

[28] Nelson H, Bleecker ER, Corren J, Yancey S, Ortega H, Reilly D, Emmett A, Anderson W. Characterization of asthma exacerbations by Arg16Gly genotype in subjects with asthma receiving salmeterol alone or with fluticasone propionate. J Allergy Clin Immunol. 2008; 121 (issue 2, supp 1): S131.

[29] Palmer CN, Lipworth BJ, Lee S, et al. Arginine-16 beta2 adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. Thorax. 2006; 61: 940-944.