



Date

IMPORTANT SAFETY INFORMATION

Direct Healthcare Professional Communication on the association of SALBUTAMOL (Ventolin) with myocardial ischaemia

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Dear Healthcare Professional:

Summary

Further to discussions with European regulatory agencies including The Irish Medicines Board, GlaxoSmithKline would like to inform you of important changes to the prescribing information for Ventolin™ (salbutamol). This information is applicable to the following formulations:

- *Ventolin™ tablets, injection and solution for intravenous infusion, for obstetric and respiratory indications;*
- *Ventolin™ Diskus™, Evohaler™, Nebules™, Syrup and Respirator solution, for respiratory indication only.*

In summary the new advice relates to:

Obstetric use in the management of premature labour:

- Salbutamol should not be used as a tocolytic agent in patients with pre-existing ischaemic heart disease (IHD) or those with significant risk factors for IHD
- Caution should be exercised when using salbutamol in women in premature labour, with supervision of cardiovascular function including ECG and discontinuation of the drug if signs of myocardial ischaemia develop.

Use in respiratory disease:

- Patients with underlying severe heart disease (e.g. IHD, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease.
- Patients should be advised to continue to use salbutamol as directed by their healthcare professional and should not stop using their medication without consulting their physician.

Further information

Background

The new advice follows a review of the available data conducted by GlaxoSmithKline of myocardial ischaemia in association with salbutamol, which considered data from the published literature, clinical trials and spontaneous reports.

Obstetric use in the management of premature labour:

The review identified a small number of cases of myocardial ischaemia suggestive of a causal association when salbutamol was given for the treatment of premature labour. This is further supported by the literature on both beta-agonists as a class and salbutamol specifically when used in the treatment of premature labour (Ref. 1-7). The available data indicates that, in women receiving intravenous salbutamol for preterm labour, salbutamol should be used with caution, due to the risk of developing myocardial ischaemia.

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For women with significant risk factors for ischaemic heart disease, the risk of myocardial ischaemia is believed to outweigh the benefits of the use of salbutamol as a tocolytic agent in the management of preterm labour, given that alternative treatments are available which do not carry a similar risk. Therefore, the product information for Ventolin is being revised to contraindicate use of salbutamol as a tocolytic agent in patients with pre-existing IHD, or those with significant risk factors for IHD.

Use in respiratory disease:

Ischaemic heart disease is prevalent in the population of patients taking beta-agonist therapy for respiratory indications. Whilst the evidence in the scientific literature, and from spontaneous reporting, is not conclusive for patients receiving salbutamol for respiratory indications, there is some evidence of myocardial ischaemia associated with salbutamol (Ref. 8 - 15). It is therefore recommended that patients with a history of severe heart disease seek medical attention if they experience symptoms suggestive of worsening heart disease. Particular attention should also be paid, particularly in patients with pre-existing cardiovascular history, to the assessment of presenting symptoms such as dyspnoea and chest pain, as they may be of either cardiac or respiratory origin.

Information about myocardial ischaemia is being added to the product information for all presentations of Ventolin. Full details of the amendments can be found in Annex 1.

Further information on recommendations to healthcare professionals

As myocardial ischaemia has been reported during or following treatment of premature labour with beta-2 agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG, should be monitored. If signs of myocardial ischaemia develop, treatment should be discontinued.

Call for reporting

Any suspected adverse reactions should be notified to Ms. Claire Finegan, Pharmacovigilance Executive, GlaxoSmithKline Ireland on 01 4955220 (Fax: 01 4938839) or the Irish Medicines Board in the usual way.

Communication information

If you have any further questions or wish to discuss this letter, please contact GlaxoSmithKline on 1800 244 255.

Yours sincerely,

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List of Literature References

- 1) James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy, a United States population-based study. *Circulation* 2006; 113: 1564-1571.
- 2) Pincus R. Salbutamol Infusion for Premature Labour – The Australian Trials experience. *Aust NZ J Obstet Gynaecol* 1981; 21: 1-4.
- 3) French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001; 98: 177-185.
- 4) Mulders LG, Boers GH, Prickartz-Wijdewald MM, Hein PR. A study of maternal ECG characteristics before and during intravenous tocolysis with beta-sympathomimetics. Effect of IV tocolysis on maternal ECG characteristics. *Acta Obstet Gynecol Scand* 1987; 66: 417-420.
- 5) Hadi HA and Alabazzaz SJ. Cardiac isoenzymes and electrocardiographic changes during ritodrine tocolysis. *Am J Obstet Gynecol*. 1989; 161: 318-321.
- 6) Arulkumaran S, et al. Myocardial strain associated with intravenous salbutamol therapy for preterm labour - ? Drug effect. Case Report. *Sing J Obstet Gynecol* 1986;17(1):54-58
- 7) Vermes E, et al. Myocardial infarction in pregnancy during treatment with salbutamol. *Arch Mal Coeur* 1997;90:1651-4
- 8) Soriano JB. Visick GT. Muellerova H. Payvandi N. Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; 128(4):2099-107.
- 9) Au, DH et al. Association between inhaled beta agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002; 121: 846-851.
- 10) Au D, Lemaitre R, Curtis J et al. The risk of myocardial infarction associated with inhaled β -adrenoceptor agonists. *Am J Respir Crit Care Med* 2000; 161: 827-830.
- 11) Suissa S, Hemmelgam B, Blais L, Ernst P. "Bronchodilators and acute cardiac death." *Am. J. Respir. Crit. Care Med*. 1996; 154: 1598-1602
- 12) Suissa, S et al. Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003;58:43-46
- 13) Craig-McFeely PM. Wilton LV. Soriano JB. Maier WC. Shakir SA. Prospective observational cohort safety study to monitor the introduction of a non-CFC formulation of salbutamol with HFA134a in England. *International Journal of Clinical Pharmacology & Therapeutics*. 41(2):67-76, 2003 Feb.
- 14) Newhouse M, Chapman K, McCallum A et al. Cardiovascular safety of high doses of inhaled fenoterol and albuterol in acute severe asthma. *Chest* 1996; 110: 595-603.
- 15) Rossinen J, Partenen J, Stenius-Aariala B, Nieminen MS. Salbutamol inhalation has no effect on myocardial ischaemia, arrhythmias and heart-rate variability in patients with coronary artery disease plus asthma or chronic obstructive pulmonary disease. *J. Int. Med*. 1998; 243: 361-366.

ANNEX 1 – DETAILS OF AMENDMENTS

Additional wording for Summary of Product Characteristics

– Salbutamol Products with both obstetric and respiratory indications

4.3 Contraindications

Salbutamol should not be used as a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.

4.4 Special Warnings and Precautions for Use

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of myocardial ischaemia associated with salbutamol.

Tocolysis

Salbutamol should be used with caution in tocolysis and supervision of cardiorespiratory function, including ECG monitoring, should be considered. Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Salbutamol should not be used as a tocolytic agent in patients with significant risk factors for or pre-existing heart disease (see section 4.3).

Respiratory indications

Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

4.8 Undesirable Effects

Respiratory indications

Unknown: Myocardial ischaemia* (see section 4.4)

* reported spontaneously in post-marketing data therefore frequency regarded as unknown

Obstetric indications

Unknown: Myocardial ischaemia*.

*In the management of pre-term labour with salbutamol injection/solution for infusion.

Additional wording for Patient Information Leaflet

– Salbutamol products with both obstetric and respiratory indications

Tell your doctor before starting this medicine:

- If you have a history of heart disease, irregular heart rhythm or angina.

Side effects:

Although it is not known exactly how often this happens, some people may occasionally experience chest pain (due to heart problems such as angina). Tell your doctor/midwife if you develop these symptoms whilst receiving treatment with salbutamol, but do not stop using this medicine unless told to do so.

Additional wording for Summary of Product Characteristics

– Salbutamol products with respiratory indication only

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