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April 2007

Dear Healthcare Professional

### IMPORTANT SAFETY INFORMATION

Further to discussions with European regulatory agencies including the Medicines and Healthcare product Regulatory Agency, GlaxoSmithKline would like to inform you of important changes to the prescribing information for Ventolin™ (salbutamol).

Please find attached a full document to explain these changes.

Healthcare Professionals wishing further information can call the GlaxoSmithKline Customer Contact Centre on 0800 221 441, between the times of Monday to Friday 8am to 6pm.

Yours faithfully

A handwritten signature in black ink, appearing to read 'Stuart Dollow', written over a white background.

Dr Stuart Dollow  
Vice President / UK Medical Director, GlaxoSmithKline

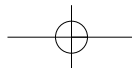
Ventolin is a trade mark of the GlaxoSmithKline group of companies.

VTN/LTR/07/30493/1

April 2007

**Registered in England & Wales**  
No. 4310159

**Registered office**  
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April 2007

**IMPORTANT SAFETY INFORMATION**  
*Direct Healthcare Professional Communication on the association of  
SALBUTAMOL (Ventolin) with myocardial ischaemia*

**Summary**

Further to discussions with European regulatory agencies including the Medicines and Healthcare product Regulatory Agency, 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™ Evohaler™, Accuhaler™, Nebules™, Respirator solution, Syrup, Ventodisks™ and Volmax™ Tablets, 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 health care professional and should not stop using their medication without consulting their physician.

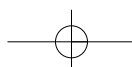
**Further information**

***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.

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.

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.



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**

Healthcare professionals and patients are requested to report serious suspected adverse reactions associated with salbutamol directly to the Medicines and Healthcare products Regulatory Agency at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). In addition, GlaxoSmithKline encourages healthcare professionals to report suspected adverse reactions, pregnancy, overdose and unexpected benefits to the company on 0800 221 441.

#### **Communication information**

Should you have any questions or require additional information, please contact the GlaxoSmithKline customer contact centre on 0800 221 441, fax 020 8990 4328 or email [customercontact@gsk.com](mailto:customercontact@gsk.com).

#### **Annexes:**

- 1) Text of the revised Product Information
- 2) List of literature references

#### **Annex 1**

#### **New text added for products with both respiratory and obstetric indications**

#### **SUMMARY OF PRODUCT CHARACTERISTICS**

##### ***4.3 Contraindications***

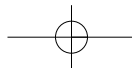
Salbutamol should not be used as a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease

##### ***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**

Frequency: Unknown - Myocardial ischaemia\* (see section 4.4)

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

##### **Obstetric indications**

Frequency: Uncommon - Myocardial ischaemia\*.

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

#### **PATIENT INFORMATION LEAFLET**

Tell your doctor before starting this medicine:

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

#### **Respiratory indications**

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.

#### **Obstetric indications**

In the management of premature labour, some people may 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.

#### **New text added for products with respiratory-only indications**

#### **SUMMARY OF PRODUCT CHARACTERISTICS**

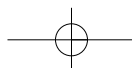
##### **4.4 Special Warnings and Precautions for Use**

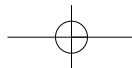
Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, 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**

Frequency: Unknown - myocardial ischaemia\* (see section 4.4)

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





## PATIENT INFORMATION LEAFLET

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.

Ventolin, Evohaler, Accuhaler, Nebules, Ventodisks and Volmax are trade marks of the GlaxoSmithKline group of companies.

## Annex 2

### 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.
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- 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.

