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27th November 2013

Short-acting beta agonists in obstetric indications: Important restrictions on use

Dear Healthcare Professional,

Actavis UK Ltd, the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following important restrictions regarding the use of short-acting beta agonists (SABAs) in obstetric indications:

Summary

- **Oral and suppository SABAs should NOT be used in any obstetric indication.**
- **The use of parenteral SABAs should be limited to 48 hours maximum and administered under specialist supervision in all authorised obstetric indications:**
  - **Inhibition of premature labour between 22 and 37 weeks of gestation**
  - **External cephalic version**
  - **Emergency use in specified conditions**
- **SABAs are associated with serious, sometimes fatal, adverse cardiovascular events in both the mother and the foetus/newborn.**

The restrictions above refer to Salbutamol 2mg and 4mg tablets.

Further information

Following reports of serious and fatal cardiovascular events including myocardial ischaemia and pulmonary oedema in association with obstetric use, the Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA reviewed the balance of benefits of risks of all SABAs in the obstetric indications. The conclusions and implications are outlined below:

Oral and suppository SABAs

The SABAs are associated with serious and dose dependent adverse events, predominantly cardiovascular, that are observed in both the mother and foetus. There is insufficient evidence to support the use of prophylactic oral betamimetics for preventing preterm birth in women at high risk of preterm labour with a singleton or twin pregnancy. No statistically significant effect of tocolysis on perinatal mortality or morbidity has been observed in randomised, controlled trials.

The benefits of oral SABAs do NOT outweigh the risks in obstetric indications and therefore should no longer be used. The obstetric indications will be removed from all oral SABA licences

Parenteral SABAs

Parenteral SABAs are efficacious in the rapid relaxation of the uterus. Women most likely to benefit from the use of tocolytic drugs are those who are at very preterm labour. The delay in

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preterm labour achieved may be used to implement other measures known to improve perinatal health. (1, 2)

Similarly, the use of SABAs in emergency conditions and to enable external cephalic version (ECV) is supported as this reflects limited duration of use, and minimal dosing.

PRAC has concluded that the benefits of parenteral SABA formulations exceeds the risks in the obstetric indication of tocolysis in the short-term – maximum of 48 hours for patients between 22 and 37 weeks of gestation and under specialist supervision.

In order to minimise and manage risk to mothers and the foetus, PRAC also recommended that use in tocolysis should be subject to appropriate pre-treatment screening and patient monitoring, in particular should the mother and foetus continually be monitored in order to identify the early onset of cardiovascular events and further minimise risk of a serious cardiovascular event. SABAs should not be used in women with a history of heart disease or in conditions of the mother or foetus in which prolongation of the pregnancy is hazardous.

Call for reporting
Healthcare professionals should report any adverse events suspected to be associated with the use of SABAs according to national reporting requirements.
Report adverse events to either the MHRA via the Yellow Card Scheme:
www.mhra.gov.uk/yellowcard

Or directly to the MAH:
Medical Information Team
RPM, Actavis UK Ltd
Whiddon Valley, Barnstaple
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Tel: +44 (0)1271 385257
Email: medinfo@actavis.co.uk

Company contact point
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Sincerely,

LHughes

Mrs Lisa Hughes
Medical Affairs Manager

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References:

1. RCOG Green-top guideline No 1b (2011). Tocolysis for women in preterm labour. http://guideline.gov/content.aspx?id=25674#Section420

2. McParland PC. Obstetric management of moderate and late preterm labour. Seminars in Fetal and Neonatal Medicine 2012; 17:138-142