2nd October, 2013

Direct Healthcare Professional Communication

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

Dear Healthcare Professional,

Remedica Ltd, the European Medicines Agency (EMA) and the Medicines Authority of Malta 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**
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- **SABAs are associated with serious, sometimes fatal, adverse cardiovascular events in both the mother and the foetus/newborn.**
- **Parental 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**.

The restrictions above refer to terbutaline,salbutamol, hexoprenaline, ritrodine, fenoterol and isoxsuprine.Remedica's authorised pharmaceutical product in Malta that contains a short-acting beta agonist (SABA) is included in Annex 1.

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:
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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 and suppository 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 or suppository 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 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. *(To be retained only where currently authorized)*

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.

Extract from the Summary of Product Characteristics (SmPC) for SABAs with an obstetric indication for tocolysis is annexed. *[Optional, since translated SmPC is probably not available in all MS at the time for distribution of the letter]*

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of SABAs according to national reporting requirements.

Healthcare professionals are hence requested to submit ADR reports using the ADR report card which can be found at http://medicinesauthority.gov.mt/reportingadversereactions?l=1 and submit it electronically to postlicensing.medicinesauthority@gov.mt or by post to 'Medicines Authority, 203, Level 3, Rue D'Argens, Gzira GZR1368'.

Company contact point

For further medical information on SABAs, please contact Remedica Ltd on +357 25 553251 or DrugSafety@remedica.com.cy and/or to Vivian Corporation Ltd. on +356 21320338/21344610/21344616 or pv@viviancorp.com .

Sincerely,

Christina Cachia
Medical Representative
Vivian Corporation

Andreas Vasiliou
European Union Qualified Person for Pharmacovigilance
(EU QPPV), Remedica Ltd

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

ANNEX 1: Pharmaceutical product of Remedica Ltd that contains a Short Acting Beta Agonist

Trade Name	Active Substance	Strength	Pharmaceutical form
Salbutamol	Salbutamol	4mg	Tablets