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Restrictions on use of short-acting beta-agonists in obstetric indications – CMDh endorses PRAC recommendations

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)¹ has endorsed by consensus new recommendations to restrict the use of medicines called ‘short-acting beta-agonists’. These medicines should no longer be used in oral or suppository forms in obstetric indications (for the care of pregnant women), such as for suppressing premature labour or excessive labour contractions. However, injectable forms of these medicines can still be given for short-term obstetric use under specific conditions.

These recommendations follow a review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), which looked into the known risk of cardiovascular side effects (problems affecting the heart and blood vessels) with high doses of short-acting beta-agonists when used as tocolytics (medicines that suppress labour contractions).

The PRAC concluded that there was a risk of serious cardiovascular side effects to both the mother and unborn baby when high-dose short-acting beta-agonists are used in obstetric indications, with the data suggesting these mostly occur with prolonged use. Given the cardiovascular risk and the very limited data on the effectiveness of the oral and suppository forms of these medicines, the PRAC concluded that their benefit-risk balance is not favourable and these medicines should no longer be used in obstetric indications.

In addition to oral medicines and suppositories, this review also covered injectable short-acting beta-agonists used as tocolytics. The available data showed that injectable forms are effective at suppressing labour contractions in the short term (up to 48 hours). This timeframe can allow healthcare professionals to take other measures known to improve the health of the baby around the time of birth. Therefore, the PRAC concluded that the benefits of injectable forms of these medicines continue to outweigh their risks when used under specific conditions: these medicines should only be used to suppress premature labour for up to 48 hours, between the 22nd and the 37th weeks of pregnancy and under specialist supervision with continuous monitoring of the mother and the unborn baby. In countries where injectable forms are also authorised for external cephalic version (a method for moving the baby into the right position for birth) and emergency use in specific conditions, the PRAC

¹ The CMDh is a medicines regulatory body representing the European Union (EU) Member States



recommended that they remain authorised in these indications. It proposed revising their prescribing information, with reinforced warnings on the cardiovascular risks.

As the PRAC recommendations have been endorsed by consensus by the CMDh, they will now be implemented directly in all Member States, according to an agreed timetable. Healthcare professionals will be informed in writing of the updated recommendations. Oral and suppository formulations which are only authorised in obstetric indications will have their marketing authorisations revoked and shall be removed from the market by the Marketing Authorisation Holders by 25th November 2013 at the latest.

Information to patients

- Because of a risk of problems affecting the heart and circulation to both the mother and unborn baby with high-dose short-acting beta-agonists, these medicines must not be used by mouth or as suppositories to suppress premature labour in pregnant women.
- These medicines can still be given intravenously (into a vein) to suppress premature labour, but their use is limited to a maximum of 48 hours, and only in women between the 22nd and the 37th weeks of pregnancy.
- If you are given these medicines for premature labour in this way, your doctor will monitor you and your baby during treatment and stop treatment if there are any signs of heart problems.
- Although these medicines are also used for the treatment of asthma, they are usually given at lower doses for this condition; if you are being treated with short-acting beta-agonists and have any questions or concerns about your treatment, speak to your doctor or pharmacist.

Information to healthcare professionals

- High-dose short-acting beta-agonists are associated with a risk of serious adverse cardiovascular events to both the mother and the fetus, particularly when used for a prolonged period of time.
- Given the identified cardiovascular adverse reaction profile and the very limited data supporting the benefits of oral forms and suppositories as short or long-term tocolytics, these formulations should no longer be used in any obstetric indication.
- Parenteral short-acting beta-agonists are effective in the short-term and they can still be used in all authorised obstetric indications (inhibition of premature labour, external cephalic version, emergency use in specified conditions). However, their use should be limited to pregnant women between 22 and 37 weeks of gestation and women receiving these medicines should be kept under specialist supervision for the duration of treatment, which is limited to a maximum of 48 hours.
- Parenteral short-acting beta-agonists should not be used in women with a history of heart disease or significant risk factors for heart disease or when prolongation of the pregnancy is hazardous to mother or fetus.

These recommendations follow a review of available cardiovascular safety data on the medicines fenoterol, hexoprenaline, isoxsuprine, ritodrine, salbutamol and terbutaline when used in obstetric indications. The reviewed data originated from clinical studies, post-marketing reports and the published literature.

More about the medicine

Short-acting beta-agonists have been authorised by national procedures in several European Union (EU) Member States, and have been marketed for many years under various trade names. The medicines included in the EU review are: fenoterol, hexoprenaline, isoxsuprine, ritodrine, salbutamol and terbutaline, which have been authorised for tocolytic treatment (to suppress labour contractions). They are available as tablets, oral solutions, solutions for injection or infusion, and suppositories.

Short-acting beta-agonists work by stimulating a receptor on the surface of cells called the 'beta-2 adrenergic receptor', which brings about smooth muscle relaxation. Smooth muscle is found in many organs, including on the inner linings of the airways, blood vessels, stomach and gut, and womb. The medicines are called 'short acting' because they work quickly, usually having an effect in less than five minutes, which lasts for several hours.

More about the procedure

The review of short-acting beta-agonists was initiated in November 2012 at the request of the Hungarian medicines agency, under Article 31 of Directive 2001/83/EC.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As short-acting beta-agonists are all authorised nationally, the PRAC recommendations were sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, it will be directly implemented by the Member States where these medicines are authorised.

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