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PRAC recommends restricted use of short-acting beta-agonists in obstetric indications

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that medicines called 'short-acting beta-agonists' 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 should remain authorised for short-term obstetric use under specific conditions.

Short-acting beta-agonists cause internal muscle called 'smooth muscle' to relax. Since this relaxes the womb muscle, some of these medicines have been approved in certain EU countries as tocolytics (medicines that suppress labour contractions). At lower doses, short-acting beta-agonists are also widely used to treat asthma, as they widen the airways making it easier to breathe.

There is a known risk of cardiovascular side effects (problems affecting the heart and blood vessels) with high doses of short-acting beta-agonists. These vary from common problems such as tachycardia (rapid heartbeat) and other cardiac arrhythmias (irregular heartbeat) to serious events such as pulmonary oedema (fluid accumulation in the lungs). As a result, the medicines used in obstetric indications already carry safety warnings in their prescribing information and must not be used in patients with a history or a risk of cardiovascular disease.

Concerns were raised about the cardiovascular risk of the medicines when used as tocolytics compared with their benefit, particularly if used for a prolonged period (more than 48 hours).

The PRAC assessed the available data from clinical studies, post-marketing reports and the published literature, and considered the relevant treatment guidelines. It concluded that there was a risk of serious cardiovascular side effects to both the mother and unborn baby when 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 supporting the benefits of oral forms or suppositories as short- or longer-term tocolytics, the PRAC concluded that their risks were greater than the benefits in obstetric indications and recommended that they should no longer be used in this setting.

The available data showed that injectable forms are effective at supressing 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 outweighed the cardiovascular risks in specific conditions. They should

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be used to supress premature labour for no more than 48 hours, between the 22nd and 37th weeks of pregnancy, under specialist supervision with continuous monitoring of the mother and 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 recommended that they remain authorised in these indications. It proposed revising the prescribing information, with reinforced warnings on the cardiovascular risks. Healthcare professionals will also be informed in writing of the updated recommendations.

The PRAC recommendation will be considered by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) at its meeting on 16-18 September 2013. Patients who have any questions should speak to their doctor or pharmacist.

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 reproductive organs. The medicine's effect in asthma is due to its causing the airways to widen and making it easier to breathe. 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 at the request of the Hungarian medicines agency, under Article 31 of Directive 2001/83/EC.

The review was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As the review only covers nationally authorised medicines, the PRAC recommendation will now be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a medicines regulatory body representing the EU Member States.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

A previous review was carried out in 2006 by the former Pharmacovigilance Working Party of the European Medicines Agency, to consider the risk of myocardial ischaemia (reduced blood supply to the heart muscle) with short-acting beta-agonists. This led to the warnings and contraindication be included in the prescribing information for these medicines with regard to their use as tocolytics.

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