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NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER – 44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EC made by Hungary

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	Tablets, solutions for injection, and suppositories
Active Substance(s)	Short Acting Beta Agonists: Terbutaline Salbutamol Hexoprenaline Ritodrine Fenoterol Isoxsuprine
Marketing Authorisation Holder(s)	Various

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Short-acting beta-agonists (SABAs) are very commonly used for the treatment of asthma across Europe with a well recognised safety profile. However, SABAs are also approved for use as tocolytic agents to suppress premature labour.

Previous Europe wide review of the risk of myocardial ischaemia associated with the use of SABAs in respiratory and obstetric indications, in 2006, led to warnings in the product information that these products should be used with caution in tocolysis, and that these products are contraindicated in tocolysis in patients with pre-existing cardiovascular disease or risk factors for cardiovascular disease. More recently in 2011 a review by the US Food and Drug Administration (FDA) resulted in a Drug Safety Communication (http://www.fda.gov/Drugs/DrugSafety/ucm243539.htm). This communication stated that terbutaline injection should not be used in pregnant women for the prevention or prolonged treatment (beyond 48-72 hours) of preterm labour because of potential for serious maternal heart problems and death. The FDA further recommended that oral terbutaline should not be authorised for use in tocolysis because of a lack of efficacy in addition to the adverse cardiovascular effects.

As the FDA review had considered more recent post-marketing data, and given that the previous Europe wide review had not made any recommendations on the need to restrict the indication or duration of use of any SABA in tocolysis, it was agreed that this issue should be further reviewed by the Pharmacovigilance Working Party (PhVWP). The products evaluated in this review were salbutamol, fenoterol, terbutaline and ritodrine. Hexoprenaline and isoxsuprine were not included in this preliminary review as no information was available that time whether these products were still available for use in the EU.

The PhVWP review concluded that efficacy had been established in the short-term (up to 48 hours) with the parenteral solutions. However, there is no perceived benefit provided from maintenance therapy with the oral tablet or suppository formulations. The SABAs were also shown to be associated with a significant number of adverse events, including serious cardiovascular adverse events, which were frequently the cause of cessation of tocolytic therapy.

The preliminary recommendations of the PhVWP were that the balance of benefits and risks for the oral tablets and suppositories was not favourable, whilst the parenteral use of SABAs was favourable if use was restricted to the first 48 hours and was under specialist supervision with continued patient monitoring. PhVWP also agreed that a more comprehensive review of the available data would be important in order to determine the optimal period within gestation during which tocolytic therapy is most beneficial and to consider the balance of benefits and risks of all SABAs (including hexoprenaline and isoxsuprine) in all authorised obstetric indications, including external cephalic version and uterine hyperactivity.

In considering the most appropriate procedure by which to address this issue, we have taken into account the general clinical background familiarity with the safety profile of SABAs, the decreasing market uptake of the non-inhaled systemic formulations in recent years, and current national clinical guidelines which recommend that maintenance of tocolysis is of little benefit to the mother or pregnancy outcome. Furthermore, the product information for SABAs already advises caution in relation to use in tocolysis and contraindicates use in tocolysis in those with pre-existing cardiovascular disease or risk factors for cardiovascular disease.

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In light of the above Hungary therefore considers that it is in the interest of the Community to refer short-acting beta-agonists to the Pharmacovigilance Risk Assessment Committee (PRAC) and requests that it gives its recommendation under Article 31 of Directive 2001/83 EEC, on whether the balance of benefits and risks is positive in the management of tocolysis and other obstetric indications and whether the Marketing Authorisations for medicinal products containing short-acting beta-agonists should be maintained, varied, suspended or withdrawn.

Signed .... [redacted] Date 27th November 2012

Dr Hilda Kőszegi - Szalai
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