Annex II

Scientific conclusions and grounds for revocation or variation as applicable to the terms of the marketing authorisations and detailed explanation for the differences from the PRAC recommendation

Scientific conclusions and grounds for revocation or variation as applicable to the terms of the marketing authorisations and detailed explanation for the differences from the PRAC recommendation

The CMDh considered the below PRAC recommendation dated 5 September 2013 with regards to the terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol and isoxsuprine containing medicinal products:

1. Overall summary of the scientific evaluation of terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol and isoxsuprine containing medicinal products by PRAC (see Annex I)

On 27 November 2012, further to evaluation of data resulting from pharmacovigilance activities, Hungary informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration that the risk-benefit balance of short-acting beta-agonists (SABAs) containing medicinal products authorised in obstetric indications has become unfavourable, taking into account the cardiovascular events reported. Hungary considered it was in the interest of the Union to refer the matter to the PRAC and expressed concerns with regards to the posology and warnings reflected in the product information.

The short-acting beta-agonists (SABAs) (also known as beta-mimetics), salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine are all nationally authorised and have been on the market within the EU since the 1960s.

Authorised obstetric indications for SABAs differ across Member States. The authorised obstetric indications include partus prematurus, tocolysis (for some products use is restricted to particular weeks of gestation but for others no specific gestation period is specified), external cephalic version (ECV), and hyper-uterine contractility. Fenoterol also contains descriptions of emergency uses in the indications such as dystocias in the dilation and expulsion stages of labour (such as uterine hyperactivity or spasm occurring either spontaneously or as a result of mechanical obstruction or over stimulation by oxytocic agents); intrauterine asphyxia (as indicated by signs such as foetal heart rate decelerations or incipient to moderate foetal acidosis); obstetric emergencies (such as cord prolapse or imminent uterine rupture); uterine relaxation in acute indications such as caesarean section. Isoxsuprine and hexoprenaline tablets also have ‘threatened abortion’ within the indications and a posology for prophylaxis of labour. Both formulations of hexoprenaline are also indicated for immobilisation of the uterus pre, during and post cerclage surgery.

During this review, data from clinical studies, post-marketing reporting and published literature, including relevant treatment guidelines, have been assessed. Oral, parenteral and suppositories formulations have been included in this assessment. There are no formulations for inhalation authorised in obstetric indications.

Safety

Previous safety reviews have highlighted the risk of myocardial ischaemia associated with the use of SABAs in obstetric indications and that these products should be used with caution in tocolysis, and other obstetric indications. This review by PRAC assessed all existing data in terms of safety of

cardiovascular events when in use in these indications and the outcome of the review is summarised below.

Salbutamol

The review of all cardiovascular events for salbutamol showed this medicinal product can induce serious cardiovascular adverse events, which can result in the death of the mother and/or foetus. A total of 98 reports which included cardiovascular events were identified, the majority of which were cardiac arrhythmias, such as, tachycardia or palpitations. Two of the reports of tachycardia developed further and were fatal. There were a number of reports of pulmonary oedema contributing to the events and one case reported pulmonary oedema in association with cardiomegaly, after taking a course of tablets for five weeks, when tocolysis failed. Two cases of tocolysis maintained with suppositories only were also reported to develop pulmonary oedema. The PRAC noted eight infant fatalities, two of which were in association with pulmonary oedema and cardiovascular events. Many of these reports occurred in association with both salbutamol intravenous (i.v.) and oral salbutamol; it would appear that this adverse event is not specific to a particular formulation.

Fenoterol

A review of safety data for fenoteral showed that the cardiovascular events tachycardia and palpitations were frequently reported in clinical studies and are listed as very common side effects of the drug. In 10 clinical studies comprising 425 pregnant women, angina pectoris and arrhythmia were reported only in one case each. Myocardial infarction or serious arrhythmias were not reported in the clinical trial reports available to the MAH. Approximately 9% of the 425 women in these trials were exposed to the oral formulation and approximately 2% of the reported adverse events were associated with the oral formulation of the drug. Tachycardia, palpitations, and changes of blood pressure accounted for about 2/3 of the adverse events associated with the oral formulation.

Terbutaline

Safety data from MAH clinical trials and meta-analyses of well-designed clinical trials have been assessed. However these data only gave limited safety information. Hibbard (1996) performed a case-control study to investigate whether there is an association between long-term oral terbutaline use and *peripartum* cardiomyopathy. Four patients with no pre-existing cardiac pathology developed *peripartum* cardiomyopathy while on prolonged oral terbutaline for various treatment durations (9.5-53 days). Even after correction of potentially confounding variables, the relationship remained significant between long-term oral terbutaline therapy for preterm labour and subsequent *peripartum* cardiomyopathy.

Published studies deliver conflicting results and interpretations on the safety of terbutaline (and beta agonists) in tocolysis. Occurrence of typical adverse effects characteristic of beta receptor stimulation are well documented, and range from mild and transient discomfort to serious cardiovascular side effects requiring prompt medical intervention, e.g. in case of arrhythmias or pulmonary oedema. There is hardly any evidence of maternal death in these studies and very limited data on adverse foetal outcomes (e.g. tachycardia, hyperinsulinaemia).

Eight cases of neonatal/foetal death including abortions have been identified by the MAH. Information on fatal foetal or neonatal conditions was not sufficient to draw any conclusions on the association with intrauterine exposure to terbutaline. Furthermore, premature delivery is an established risk factor of neonatal morbidity and mortality.

Regardless of this, 18 serious cardiovascular cases have been identified in EudraVigilance showing that, not only predisposed, but also otherwise healthy subjects have developed serious cardiovascular

complications. This again highlights the importance of close medical surveillance during therapy, and questions the safety of outpatient tocolysis with terbutaline.

Ritodrine

The use of ritodrine is associated with risks of major cardiac and pulmonary dysfunction (rarely myocardial infarction), alteration in glycaemia and blood potassium concentration, gastro-intestinal disorders, tremors, headache and erythema. More rarely, cases of anxiety, dizziness, blood dyscrasias, rhabdomyolysis, severe cutaneous adverse reactions (SCARs), and anaphylactic shock have been described. The seriousness of AEs seems to be directly related to the dose of ritodrine administered to the patient, but also to the treatment duration as most of life-threatening AEs occurred after prolonged ritodrine administration (>72h to months).

During the period 2002-2012, a total of 210 cases including at least one adverse event after ritodrine treatment were reported. These cases of adverse events under ritodrine therapy included both well-documented case reports from the literature and cases recorded by the MAH from spontaneous reporting from healthcare personnel or Health Authorities. With the exception of reports on rhabdomyolysis and SCARs, the cases were mostly in accordance with the known safety profile of ritodrine.

Hexoprenaline

According to the published studies intravenous administration of hexoprenaline is very commonly accompanied with occurrence of adverse drug reactions. Maternal tachycardia is the most commonly reported adverse reaction following intravenous hexoprenaline administration. Maternal hypotension, palpitations, tremor, flush, sweating, headache and nausea also occurred commonly. More serious adverse drug reactions have been recorded individually – chest pain, dyspnoea, ileus, loss of consciousness, arrhythmia and also several case reports of pulmonary oedema (four in a publication by Van Iddekinge *et al*., 1991, one in the EV database, four in the PSUR) have been reported. In contrast to other SABAs, no maternal fatality and no case of myocardial infarction have been reported following hexoprenaline administration for tocolysis.

For oral hexoprenaline there are very few safety data. One case report of uterine haemorrhage exists however it is confounded by concomitant uterine pathology.

Isoxsuprine

Post-marketing data were summarised for isoxsuprine from 2000 to 2013; no serious AEs were reported for the i.v. product, and three non-serious events were reported. For the oral tablet, three serious AEs were reported (loss of consciousness, trismus and a serious skin reaction), and six non-serious AEs for the tablet.

Overall safety conclusions

Based on all data available for all SABAs considered in this review (terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol, isoxsuprine), there is evidence that oral and suppository formulations are associated with serious and dose dependent adverse events.

With injectable formulations there are safety issues during prolonged use of these active substances in the context of the obstetric indications, however there may be benefit in administering parental formulations in the obstetric indication of tocolysis in the short-term (maximum 48 hours). The risk to the mother and foetus could be minimised if active substances are administered by obstetricians/physicians experienced in the use of tocolytic agents.

Oral formulations and suppositories are used for the maintenance in tocolysis after the injectable forms have been administered, and considering the cardiovascular safety profile, the PRAC considers that these medicinal products no longer demonstrate a favourable benefit-risk balance.

For the parenteral formulations, the PRAC having considered all the available data and specifically for the management of uncomplicated premature labour recommends that these active substances should be given for short term management (up to 48 hours) between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy. In addition specific guidance on the method of administration should be given for these injectable formulations. Treatment should be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetus health status. These should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contra-indications of use. This should include an adequate assessment of the patient's cardiovascular status with monitoring by electrocardiogram (ECG) throughout treatment in order to identify the early onset of cardiovascular events and further minimise the 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. Careful control of the level of hydration is essential to avoid the risk of maternal pulmonary oedema.

The use of SABAs in emergency conditions and to enable external cephalic version is supported as this reflects limited duration of use and minimal dosing, and from a safety perspective these indications should be maintained, where authorised.

Efficacy

Salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine are authorised in obstetric indications since the 1960s.

Data available from clinical trials, post-marketing reports and literature were considered in this review. The PRAC identified serious limitations of the efficacy data for oral and suppository formulations, and noted the available new evidence and/or current medical knowledge on the use of these products for obstetric indications. Having considered the cardiovascular adverse reactions profile associated with the use of these medicinal products in obstetric indications, the PRAC concluded that oral forms and suppositories should no longer be used to supress contractions of the womb. Some of the products for oral use or suppositories referred in this procedure are authorised only in obstetric indications. Removal of these indications as per the PRAC recommendation will result to the revocation of these marketing authorisations. For these specific products a recall of the products is being recommended by the PRAC.

The available data showed that injectable forms are effective at supressing labour contractions in the short term (up to 48 hours). For these indications which include short term management of uncomplicated tocolysis the PRAC recommended the parenteral products should only be administered for short term management (up to 48 hours) of the obstetric indications in patients between 22 and 37 weeks of gestation. The duration of treatment should not exceed 48 hours as data show that the main effect of tocolytic therapy is a delay in delivery of up to 48 hours. This delay may be used to administer glucocorticoids or to implement other measures known to improve perinatal health. The PRAC as well recommended that the use of the parental formulations for ECV and emergency is considered favourable where these indications are already authorised.

With regards to the window of lowest gestational viability, the PRAC noted an epidemiological review of obstetric interventions in European countries (Kollée *et al*, 2009) andmore recently by US (Kyser *et al.*,

2012) which suggests it is between 22 and 24 weeks. Therefore, in order to help optimise safe and effective use, the gestational age should be reflected in the indication

The PRAC concluded that the benefits of injectable forms outweighed the cardiovascular risks in restricted conditions of use: these active substances should be given for short term management (up to 48 hours) between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy.

As part of the risk minimisation measures the PRAC proposed revised indications for the parenteral formulations taking all the data into account, and making clear the conditions for which these products are indicated. The use should be contraindicated in patients at a gestational age less than 22 weeks, in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease and in patients with threatened abortion during the first and second trimester of gestation. The committee also stressed that in the patients receiving these parenteral medicinal products the blood pressure and heart rate, electrolyte and fluid balance, glucose and lactate levels and potassium levels should be continuous monitored.

Benefit-risk balance

Having noted the above, the PRAC concluded that the benefit-risk balance is not favourable for the oral formulations and suppositories in view of the overall available safety data, in particular in relation to the risk of serious cardiovascular events, and limited efficacy. Therefore these medicinal products should no longer be indicated in the obstetrics therapeutic indication. The product information for these medicinal products should be updated accordingly; therefore these marketing authorisations should be varied. Products for which the oral and suppository formulations are only used in obstetric indications should have their licenses revoked and recalled from the market.

With regards to parenteral SABAs (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products in the obstetric indications, the PRAC concluded that the benefit-risk balance is favourable as the benefits continue to outweigh the risks. For these indications which include short term management of uncomplicated tocolysis the PRAC recommended the parenteral products should only be administered for short term management (up to 48 hours) in patients between 22 and 37 weeks of gestation. The PRAC as well recommended that the use of the parental formulations for ECV and emergency is considered favourable where these indications are already authorised. Patients should be closely monitored for signs of cardiovascular adverse reactions throughout treatment. Parenteral medicinal SABA products should be contraindicated in patients at less than 22 weeks of gestation, in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease and in patients with threatened abortion during the first and second trimester of gestation. In addition, blood pressure and heart rate, electrolyte and fluid balance, glucose and lactate levels and potassium levels should be continuously monitored.

The Committee concluded that there was a need for further risk minimisation measures to inform healthcare professionals of the new restrictions on use and monitoring requirements introduced to ensure safe use of the parenteral formulations in the obstetric indications and to inform of the unfavourable benefit-risk balance of the oral and suppositories formulations in these indications.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for short-acting beta-agonists (SABAs) (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products in the obstetric indications (see Annex I).
- The Committee reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature and post-marketing experience on the safety of short-acting beta-agonists (SABAs) (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products in the obstetric indications.
- The Committee is of the opinion that the benefits of the parenteral formulations of short-acting beta-agonists (SABAs) (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products continue to outweigh the risks in the obstetric indications of short term management of uncomplicated tocolysis.
- The Committee in addition stressed that the parenteral products should only be administered for short term management (up to 48 hours) of the obstetric indications in patients between 22 and 37 weeks of gestation. Patients should be closely monitored for signs of cardiovascular adverse reactions throughout treatment.
- The Committee considered that in view of the currently available safety data in order to maintain a favourable benefit-risk balance, these parenteral SABAs (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products should be contraindicated in patients at a gestational age less than 22 weeks, in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease and in patients with threatened abortion during the first and second trimester of gestation. The committee also stressed that in the patients receiving these parenteral medicinal products the blood pressure and heart rate, electrolyte and fluid balance, glucose and lactate levels and potassium levels should be monitored throughout treatment.
- For the oral and suppositories formulations in view of the overall available safety data, in particular in relation to the risk of serious cardiovascular events, and very limited efficacy data, the PRAC concluded in accordance with Article 116 of Directive 2001/83/EC that the benefit-risk balance is not favourable and therefore these medicinal products should no longer be indicated in the obstetrics therapeutic indication.
- The Committee concluded that there was need for further risk minimisation measures such as information to healthcare professionals to inform on the outcome of the review and the safe use of the parenteral formulations in the obstetric indications.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the variation to the terms of the marketing authorisations, or revocation, as applicable, for all medicinal products referred to in Annex I and for which the amendments to the product information are set out in Annex III of the recommendation.

a. Oral and suppository formulations which are only authorised in the indications proposed to be removed (in accordance with changes to the product information as set out in Annex III) should

have their marketing authorisations revoked and should be recalled within given deadlines. The conditions for the revocation of the marketing authorisations of these products, as applicable, are set out in Annex IV.

b. All other marketing authorisations of SABAs (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products indicated in tocolysis and other obstetric indications (see Annex I) should be varied (in accordance with changes to the product information as set out in Annex III).

c. All marketing authorisation holders should implement risk minimisation measures.

2. Detailed explanation for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, the CMDh considered that a minor change was necessary to the wording proposed in the conditions to the Marketing Authorisations (Annex IV). The CMDh proposed to shorten the time for recall of the products with only obstetric indications and for which revocation is applicable to ensure that prompt action is taken on products with no marketing authorisation.

CMDh Agreement

The CMDh, having considered the PRAC recommendation dated 5 September 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached an agreement on the variation or revocation as applicable of the marketing authorisations of terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol and isoxsuprine containing products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.

The timetable for the implementation of the agreement is set out in Annex V.