EUROPEAN MEDICINES AGENCY
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Assessment report for Short Acting Beta Agonists (SABAs) containing medicinal products authorised in obstetric indications

Procedure under Article 31 of Directive 2001/83/EC

INN/active substance: terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol, isoxsuprine

Procedure number: EMEA/H/A-31/1347

Assessment Report as adopted by PRAC with all the information of a confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure

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 a 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.

2. Scientific discussion

The short-acting beta-agonists (SABAs), salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine are all nationally authorised and have been on the market within the EU for several decades. Oral, suppository and parenteral formulations exist but the types of formulations that are available for the different SABAs differ between European countries.

Authorised obstetric indications for SABAs differ across Member States. Across Europe, 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 and salbutamol also contain 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 (oral and parenteral) of hexoprenaline are also indicated for immobilization of the uterus pre, during and post cerclage surgery.

During this review, data regarding the cardiovascular events from clinical studies, post-marketing reporting and published literature have been assessed. All formulations, oral (tablets including modified/prolonged released tablets, oral solutions), parenteral and suppositories have been included in this assessment. There are no inhaled formulations that have authorised obstetric indications.

2.1. Clinical aspects

2.1.1. 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.

Patient exposure

Data on patient exposure available was generally derived from sales figures of the different formulations. However it was concluded that these data did not allow a reliable estimate of obstetric use to be determined and they only provided a general trend in usage of the non-inhaled formulations. A trend of decreased usage of these products was noted.

Post-marketing reporting of cardiovascular events

A review of all cardiovascular events reported was undertaken for each substance. A summary for each substance is presented hereinafter.

Salbutamol

The review of all cardiovascular events for salbutamol showed this medicinal product can induce serious cardiovascular adverse events, which in some cases resulted in the death of the mother and/or foetus. A cumulative search of the MAH database in February 2012 for cardiovascular adverse events in pregnant patients receiving a non-inhaled salbutamol formulation revealed 98 reports, the majority of which were cardiac arrhythmias, such as, tachycardia or palpitations. In two of the reports of tachycardia the patients developed more serious reactions which were subsequently fatal. One of these cases involved a woman receiving tocolysis via salbutamol infusion at 38 weeks gestation. The reason for tocolysis at this late stage of gestation is unknown. However, the cardiovascular reports also included more imminently serious reactions such as myocardial ischaemia, myocardial infarction, and pulmonary oedema, which are life threatening, and also resulted in a further two fatalities. There were a number of reports of pulmonary oedema contributing to the events, which is listed in the summary of product characteristics (SmPC) as an adverse event with a frequency of uncommon for the solutions for injection/infusion but not for the tablets. Considering that tablets or suppositories are generally only used for maintenance in association with an intravenous (i.v.) treatment regimen, it is not likely that many reports of pulmonary oedema solely in association with either tablet or suppository would be reported. One case reported pulmonary oedema in association with cardiomegaly, after taking a course of tablets for five weeks, and re-starting a salbutamol infusion when premature labour resumed. Two cases of tocolysis maintained with suppositories only may have also developed pulmonary oedema.

It was noted that the reported cardiovascular events are listed in the product information. The warnings that patients should be monitored for cardiovascular events during treatment, with consideration of withdrawing treatment should the events become serious or deleterious to either mother or child, are currently reflected in the SmPC. However, there is no consideration of optimal duration of use.

There were concerns about the events of pulmonary oedema. Four maternal fatalities are reported in this review in association with i.v. salbutamol with associated cardiovascular events or pulmonary oedema. There were also 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 i.v. and oral salbutamol, so it would appear that this adverse event is not specific to a particular formulation. It is also difficult to ascribe a specific set of adverse events to a particular formulation, as the tablet or suppository formulations are generally used following i.v. infusion for maintenance of tocolysis.

Fenoterol

A review of safety data for fenoterol 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 cardiovascular adverse events associated with the oral formulation.

A cumulative review of the MAHs post-marketing safety database identified 498 Individual case safety reports (ICSRs) in association with fenoterol. A total of 192 of these ICSRs were serious and 455 of all cases were confirmed by healthcare professionals. The three system organ classes (SOCs) with the highest numbers of cases were Respiratory, thoracic and mediastinal disorders (104 cases), Cardiac disorders (54 cases), and Nervous system disorders (52 cases). The three highest numbers of serious cases were reported in the SOCs Respiratory, thoracic and mediastinal disorders (61 cases), Cardiac disorders (23 cases), and Infections and infestations (29 cases). The distribution of cases across the SOCs was similar for both oral and i.v. products.

A total of 8 cases of myocardial infarction have been received by the MAH as well as a total of 19 cases of maternal death.

Terbutaline

A previous review in 2011 by the Food and Drug Administration (FDA) supported the introduction of new warnings and contraindications against the use of terbutaline in tocolysis, through the identification of 16 cases of maternal death during the period from its first marketing until 2009, and 12 maternal cases of serious cardiovascular events between January 2008 and July 2009. Most cases involved the prolonged administration of terbutaline either via the subcutaneous or the oral route.

Safety data from clinical trials conducted with terbutaline by the MAH were insufficient to draw any conclusions on the safety and predictability of risks associated with terbutaline, especially in terms of dose, indication (i.e. acute tocolysis, long-term maintenance treatment, repeated or prophylactic use), and underlying condition of the mother. Meta-analyses of well-designed clinical trials lack stratification of adverse maternal outcomes according to the mode and length of administration or the dose applied. Individual patient characteristics and medical conditions are poorly documented in any of the analyses, precluding identification of patient subgroups at increased risk.

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 no evidence of maternal death in these studies and very limited data on adverse foetal outcomes (e.g. tachycardia, hyperinsulinaemia).

As pulmonary oedema is a relatively rare adverse effect of terbutaline even the three large observational studies have not allowed any conclusion to be drawn as to whether pulmonary oedema is more frequent on long-term administration compared to short-term (24-48 hours) treatment. However, in combination with other tocolytics the incidence of pulmonary oedema may be more pronounced. In a study (Kosasa *et al*., 1994), in which long-term combination of i.v. magnesium and terbutaline were administered to 1000 women, 3.3% developed pulmonary oedema. No severe or irreversible consequences were recorded, as all of them received their tocolytic treatment in a hospital setting and could receive corrective treatment immediately.

Post-marketing reported cases of maternal fatalities to terbutaline used in tocolysis illustrate the need for adherence to the contraindications, warnings and precautions in the product information of terbutaline to prevent maternal deaths.

Eight cases of neonatal/foetal death including abortions have been identified by the MAH. Information on fatal foetal or neonatal conditions was not enough 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 (EV) 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.

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.

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 adverse events (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 fatalities and no case of myocardial infarction have been reported following hexoprenaline administration for tocolysis.

For oral hexoprenaline there are no safety data. One case report of uterine haemorrhage exists however it is confounded by concomitant uterine pathology.

Isoxsuprine

Isoxsuprine i.v. treatment is associated with dose-related cardiovascular side-effects, including pulmonary oedema. With an infusion rate of 0.20 mg/min, the average increase in maternal heart rate was 11% while systolic and diastolic blood pressures decreased by 8% and 6.5%, respectively. With an average infusion rate of 0.60 mg/min for an average of 5 hours, maternal heart rate increased by 34% while systolic and diastolic blood pressure decreased by 16% and 29%, respectively. Maternal pulmonary oedema has been reported with isoxsuprine treatment of preterm labour at an incidence of 0.5% (7/1407 patients) in one institution over a 7-year interval. The mean duration of therapy by infusion for the 7 patients was 4 days (range 1.7 -9.4 days) and total dose ranged from 633 to 3912 mg (mean 1834 mg) at a rate of infusion in the 24 h preceding the onset of pulmonary oedema of 0.41 mg/min.

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.

Clinical Guidelines

Clinical guidelines and references for clinical guidance have been reviewed from across the EU and from the US and Australia. Generally, all refer to the benefits of short-term tocolysis, to enable transfer of patients *in utero* to tertiary care centres, or to enable completion of antenatal steroid treatment to improve foetal lung maturity. Maintenance tocolytic therapy was not recommended on the basis of insufficient evidence of benefit.

The main tocolytic agents considered by the guidelines include beta-agonists, oxytocin antagonists (atosiban), and calcium channel blockers (nifedipine).

It was noted that no guideline specifically recommends a SABA as a first line choice for tocolysis. The preference for alternate tocolytic agents is principally based on concerns about a significant number of serious adverse events, including serious cardiovascular reactions, occurring in association with beta-agonists. Women likely to benefit from tocolysis treatment are those presenting with very pre-term labour (20-32 weeks gestation). However the upper limit of treatment according to gestational age ranges between 34 weeks and 37 weeks.

Conclusions on safety

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 is 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. 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.

2.1.2. Efficacy

The evidence of benefit of these medicines in the obstetric indications was considered, with a summary of the efficacy of the different active substances discussed below.

Salbutamol

Limited data is available on the use of oral or suppository salbutamol as a tocolytic agent. In the trials identified, oral salbutamol was mainly used for maintenance of tocolysis, and not induction of tocolysis, but one trial investigated whether oral salbutamol could be used as a prophylactic agent to extend gestation in multiple pregnancies (Gummerus *et al*., 1987). Maintenance of tocolysis by oral salbutamol and prophylactic treatment by oral salbutamol did not improve gestational age, or pregnancy outcome, and therefore provided little benefit to the mother or foetus.

The literature reports of studies examining salbutamol i.v. concluded that it is an effective tocolytic agent within the first 48 hours. Salbutamol i.v. has been shown to be equally as effective as the calcium channel blocker nicardipine administered i.v. (Trabelsi *et al*, 2008) and terbutaline (Motezedian *et al.,* 2010). There was little evidence supporting any specific method of administration of the i.v. product as bolus and intramuscular injection are rarely used.

An evaluation of corticosteroid treatment or transfer *in utero* to tertiary care on pregnancy outcome has not been evaluated, although they are generally considered to be beneficial to the outcome of preterm birth. It is not clear from the submitted data as to how many of the pregnancies also received steroid treatment. The outcomes of the pregnancy reports identified by the MAH identified that the majority of the births were premature indicating that tocolysis was only achieved for a short-term. Again, there is little evidence to support the use of oral salbutamol for maintenance therapy.

Salbutamol does not contain external cephalic version (ECV) within the indication or use in emergency situations.

Fenoterol

A review of published studies, including comparison studies and meta-analyses examining the use of beta-agonists in general, and not specifically fenoterol was performed. From the available data can be concluded that intravenous beta-mimetics are effective in prolonging pregnancy for up to 48 hours. There is little evidence to support any specific method of administration of the i.v. product, as both infusion and bolus injection were equally efficacious. Such a prolongation can be useful, e.g. in terms of more time to induce maturation of foetal lungs or to allow for transfer of the mother to a specialised centre. A few studies are reported to suggest effectiveness up to 7 days, however, the MAH did not provide a detailed analysis to substantiate a use beyond 48 hours. A Cochrane Review has highlighted that beta-mimetics decreased the number of women in preterm labour giving birth within 48 hours (RR 0.63; 95% CI 0.53 to 0.75) but there was no decrease in the number of births within seven days after carrying out a sensitivity analysis of studies with adequate allocation of concealment. There is no documented evidence for effectiveness in terms of reduced perinatal mortality or effectiveness of oral beta-mimetics for maintenance therapy after threatened preterm labour.

In addition there is no evidence to show significant benefits for maintenance therapy or evidence to support the prophylactic use of beta-mimetics during the second stage of labour.

None of the fenoterol formulations are authorised for prophylactic use or prevention of preterm labour. However, there is no time limit given in the SmPCs of the fenoterol formulations allowing for prolonged treatment (beyond 48-72 hours).

In the post-marketing database of one of the MAHs, information on duration of treatment is available for 132 cases with a variation of 1-98 days during gestational weeks 19-37. Fenoterol was used mainly during the gestational weeks 25-34. Therapy duration was greater than 2 days in 90 cases.

With regards to use in emergency obstetric indications, as may be expected the supporting studies are small and with the exception of one are all uncontrolled. Little can be determined regarding outcomes from these studies although they support acute emergency use of fenoterol where clinically indicated.

External cephalic version (ECV) is only mentioned in one SmPC, but relaxation of the uterus which is mentioned in all fenoterol parenteral SmPCs is a prerequisite for ECV where preferred to caesarean section or breech vaginal delivery. Fenoterol is described as being frequently used off-label at term or near term. In all the studies examining ECV the success rate was more than 50%, which is supportive of the use of fenoterol to allow ECV at term where clinically indicated.

Terbutaline

The MAH presented data from a total of 130 women participating in five company sponsored clinical trials. Two trials were designed to compare the efficacy and tolerability of terbutaline with another beta agonist (ritodrine) whereas in three further trials the only investigational product was terbutaline which means that no placebo-controlled studies are available. The only indication studied was arrest of threatening premature labour and maintenance of results ideally until the 36-37 week of gestation or until a defined time period (4-14 days). The company was not able to perform stratification per route of administration of terbutaline because the general therapeutic scheme in all trials was to initiate treatment of acute preterm labour parenterally (with individualised dosing based on uterine contractions and maternal side effects) which was followed by oral (or, in a few patients, subcutaneous) maintenance therapy. Only three patients received oral terbutaline as initial therapy which does not allow a reasonable assessment.

Period of gestation was defined in three out of the five studies (20-36th week and 28-36th week), and not specified in the remaining two. Success rate (efficacy) was evaluated by the number of days by which pregnancies were prolonged; however, no uniform definitions or criteria were applied. Data on pregnancy outcomes is available only in three out of the five studies. These data are very limited and are not assessed in the context of added benefit per extra pregnancy days gained.

Published comparator studies (terbutaline versus placebo, magnesium sulphate, atosiban and ritodrine) involving 497 patients of whom 246 received terbutaline treatment showed terbutaline to be superior over placebo, ritodrine and magnesium sulphate (as a trend) and comparable to atosiban regarding inhibition of preterm birth.

In three observational studies altogether 443 patients were treated with terbutaline to arrest preterm labour. No comparator groups were included except for the Wallace study where oral terbutaline was compared with placebo as maintenance therapy after labour had been controlled by intravenous terbutaline. However, the number of patients enrolled was small (altogether 14), not allowing a reasonable assessment.

Five meta-analyses on beta-mimetics in preterm labour were identified. The first meta-analysis (King *et al.,* 1988) demonstrated the efficacy of beta-mimetics in delaying delivery but the patient population which had the most expressed benefit could not be defined. It also noted that no beneficial effect regarding perinatal mortality or severe neonatal respiratory disorders could be proved. In the further analyses different classes of tocolytics were compared to each other and to placebo, respectively. In support of King and colleagues, tocolytics were demonstrated to delay premature birth by 24 and 48 hours, or as a trend by 7 days; however, the time gained was not associated with improved perinatal outcomes. All analyses emphasized the unfavourable safety profile of beta-agonists in comparison with other types of agents used for delaying birth.

The data of the largest female population with beta-agonist treatment (a total of 2408 women) has been reviewed in 2010. The gestational age varied from 20 to 37 weeks. The seventeen randomised controlled trials were performed mainly 20-30 years ago therefore no full data sets are available concerning maternal and neonatal outcomes. The authors concluded that beta-agonists are effective in delaying birth for 48 hours, sufficient time to allow the transfer of the woman to a higher level of care and to allow completion of an antenatal corticosteroid therapy to facilitate foetal lung maturation.

In the meta-analysis of Dodd and colleagues (2012) the efficacy of oral beta-mimetic maintenance therapy was studied to prevent preterm birth after threatened premature delivery. No evidence could be found to support the use of oral maintenance therapy with beta-mimetics as no differences were observed in the incidence of preterm birth or outcomes of perinatal mortality and morbidity when compared to placebo or no treatment (5 trials investigated terbutaline).

Currently, efficacy of beta-mimetics including parenteral terbutaline in delaying delivery is established and is determined in 48 hours, and the time gained should be used to transfer the pregnant women to a tertiary care centre with facilities for obstetric and neonatal intensive care and to complete a course of antenatal corticosteroids to improve neonatal outcomes as much as possible.

Evidence from randomised trials does not support the use of oral terbutaline for maintenance treatment of arrested labour. No evidence has been revealed either from the scientific literature or from marketing authorisation holder sponsored studies that terbutaline is efficacious in obstetric indications other than arresting threatening premature labour.

Ritodrine

Data available from literature confirms the efficacy of ritodrine for delaying delivery for 24–48 hours without improvement of neonatal outcome but its effectiveness for tocolysis in preterm labour is limited to short range (within 48 hours) prolongation of gestation. Ritodrine has been compared to other drug used as tocolytics, namely oxytocin receptor antagonists (atosiban), calcium channel blockers (nifedipine), nitric oxide donors (glyceryl trinitrate) and magnesium sulphate. Atosiban, glyceryl trinitrate and magnesium sulphate were found as effective as ritodrine in prolonging pregnancy in the setting of preterm labour, but these drugs resulted in fewer maternal side effects than ritodrine. For nifedipine, superiority over ritodrine with less maternal adverse events has been reported.

There is not enough evidence to support the use of oral beta-mimetics for maintenance therapy after threatened preterm labour that has successfully been treated with parenteral tocolyis.

Improvement of the external cephalic version (ECV) success rate and reduced rates of caesarean section in breech presentation have been demonstrated for parenteral ritodrine.

Limited evidence is available for the efficacy of ritodrine in hypertonia of the uterus during labour. However, there is only very limited evidence for the efficacy of the use of beta-mimetics like ritodrine in (acute) foetal distress, and foetal distress is a widely used but poorly defined term.

Two Cochrane reviews (2008, 2012) conclude that there is insufficient evidence to support or refute the use of prophylactic oral beta-mimetics for preventing preterm birth in women at high risk of preterm labour, both with a singleton and twin pregnancy.

There is no evidence for the use of betamimetics like ritodrine in the prevention of uterine contractions following surgical interventions during pregnancy, especially with respect to surgery on the reproductive organs and the abdomen.

Hexoprenaline

Limited data is available regarding efficacy and safety of oral hexoprenaline. There is very low bioavailability after oral administration compared to the intravenous bolus (according to a PK study availability is quoted as 2.1% whereas the company core safety information (CCSI) quotes bioavailability between 5-11%). Very little information is available from clinical trials or the literature. One pharmacodynamic study reported no significant differences in reduction of uterus motility following oral administration of hexoprenaline vs. placebo. In contrast to oral hexoprenaline, efficacy and safety of intravenous hexoprenaline is well documented for licensed indications except for the use pre, during and post cerclage surgery. During the authorisation procedure the applicant submitted 42 references of studies conducted with hexoprenaline. All, except two studies, were performed in women during pregnancy. Although, the majority of these studies are not controlled the results are consistent.

Isoxsuprine

According to literature, the effectiveness of tocolysis with beta-mimetics is ascertained as delaying delivery for 48 hours, up to 7 days in women with premature labour. No other benefits on pregnancy or neonatal benefits have been demonstrated (Haas *et al.,* 2012). A meta-analysis of trials examining isoxsuprine by Giorgino and Egan (2010) also supported efficacy of the parenteral isoxsuprine product.

Small randomised controlled trials involving isoxsuprine produced conflicting results, mainly owing to their small size, method of randomisation with placebo, and description of results. Oral tablets alone were not different from placebo at altering the rate of preterm births. Isoxsuprine i.v. plus oral

administration did not prolong pregnancy longer than placebo, although they were better at preventing birth, therefore providing evidence of efficacy in the acute scenario. A comparison of combination (i.v. plus oral) isoxsuprine with oral nifedipine resulted in a similar outcome in preventing preterm delivery in 27% and 34% of the cases (Rayamajhi *et al.,* 2003). However, lack of detail in the study did not allow a full evaluation of the results. The results also indicated that a successful tocolytic outcome was dependent upon cervix dilation at start of therapy, with increased success in patients with cervix dilation of less than 4 cm.

One study examined threatened abortion (Leep *et al.,* 1963), although this was not a randomised placebo controlled trial. The control group was a retrospective selected group of patients. Abortion occurred in 6/80 treated patients with isoxsuprine and in 3/320 of the untreated group (7.5% with isoxsuprine and 0.9% without), resulting in an odds risk of abortion of 8.86 (95% CI 1.85-33.04) associated with isoxsuprine treatment. Therefore there is little evidence to support the use of isoxsuprine as a treatment in threatened abortion.

No studies or literature was presented examining the efficacy of isoxsuprine in ECV or emergency situations such as uterine hyperactivity.

There is no evidence that oral tocolysis maintenance could be of benefit in reducing preterm birth. In the review by Dodd and colleagues (Cochrane Database Syst Rev 2006), 13 trials using oral ritodrine or terbutaline vs. placebo demonstrated that maintenance oral treatment with beta-mimetics performed after the resolution of preterm labour, did not prevent preterm birth, recurrence of preterm labour, recurrence of hospitalisation, perinatal morbidity or mortality. There are no trials using oral isoxsuprine that could prove otherwise.

Duration of use and methods of administration for all SABAs

During the assessment of all data submitted for this referral procedure the duration of use for all SABAs was also assessed. It was found that there are no consistent recommendations in different EU member states.

The PRAC therefore having considered all the available data and specifically for the management of uncomplicated premature labour recommends that for the parenteral formulations of these active substances they should be only given for short term between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy.

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. With regards to gestational age, although there is debate over the window of lowest gestational viability, an epidemiological review of obstetric interventions in European countries (Kollée *et al*. 2009) suggests it is between 22 and 24 weeks. Additionally, most recent data (Kyser, *et al.* 2012) indicate that neonates born at 22 weeks to mothers in pre-term labour provided with tocolysis in order to given sufficient time to administer a course of corticosteroids, is associated with a 33% survival rate. This is greater than the predicted value of 19%, and provides evidence that tocolysis at this early stage can prove useful to improve foetal survival rate by providing a window for administering corticosteroids. In light of all available data the PRAC suggested that, the gestational age should be between 22 to 37 weeks and the use should be contraindicated below 22 weeks of gestation.

In addition special cautions for infusion were given by PRAC. The dose must be individually titrated with reference to suppression of contractions, increase in pulse rate and changes in blood pressure,

which are limiting factors. These parameters should be carefully monitored during treatment. A maximum maternal heart rate of 120 beats per min should not be exceeded.

Conclusions on 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.

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 that may 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 (Kollee *et al.,* 2009) of obstetric interventions in European countries and more recent data from the US (Kyser *et al.,* 2012) which suggest it is between 22 and 24 weeks. Therefore, in order to help optimise safe and effective use, the 22 week gestational age should be reflected in the indication. Similarly in the contraindications section, use in tocolysis below 22 weeks of gestation should be included.

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.

2.2. Risk minimisation activities

As part of the routine risk minimisation measures the PRAC adopted an updated indication for the parenteral formulations as well as other sections taking all the data into account, and making clear the conditions for which these products are indicated. Oral and suppository formulations should no longer be used in obstetric indications.

In addition, the PRAC endorsed a Direct Healthcare Professional Communication (DHPC), to communicate the outcome of the present review and to inform healthcare professionals of the updated indication, the cardiovascular risks, the recommendation for short term use of these products and the revised gestational period. The information that the oral formulations and suppositories should not be further used in the obstetric indications is also conveyed.

2.3. Product information

i. The PRAC recommended that all obstetric indications and any reference to those in the Product Information should be removed in the oral formulations and suppositories.

ii. The PRAC recommended the amendments to be introduced in the summary of product characteristics (SmPC) and package leaflet of parental medicinal products for obstetric indications, as follows:

Summary of Product Characteristics

Section 4.1 - Therapeutic indications

The new proposed obstetric indications only for the parenteral formulations are as follows:

> *'For the short term management of uncomplicated premature labour*
> *To arrest labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy.*

The *'external cephalic version'* and the *'emergency use'* indications remain only in the parenteral products for which they are currently already approved.

> *External cephalic version*
>
> *Emergency use in specified conditions'*

Section 4.2 – Posology and method of administration

Updated instructions in the management of uncomplicated premature labour have been proposed in this section. The treatment should only be initiated by obstetricians/physicians experienced in the use of tocolytic agents and it should be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetus health status.

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 implement other measures known to improve perinatal health.

Treatment should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contra-indications to the use. This should include an adequate assessment of the patient's cardiovascular status by a physician experienced in cardiology with ECG monitoring throughout treatment.

Special cautions for infusion should be observed with individual dose titration with reference to suppression of contractions, increase in pulse rate and changes in blood pressure, which are limiting factors. These parameters should be carefully monitored during treatment. A maximum maternal heart rate of 120 beats per min should not be exceeded.

In addition careful control of the level of hydration is essential due to the risk of maternal pulmonary oedema and by keeping the volume of fluid in which the drug is administered to a minimum.

Section 4.3 – Contraindications

Use should be contraindicated: at a gestational age less than 22 weeks; in patients have pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease; for any condition of the mother or foetus in which prolongation of the pregnancy is hazardous, e.g. severe

toxaemia, intrauterine infection, vaginal bleeding resulting from *placenta praevia*, eclampsia or severe preeclampsia, placental abruption, or cord compression; in cases of intrauterine foetal death, known lethal congenital or lethal chromosomal malformation. In addition they should not be used during threatened abortion during the first and second trimester. Furthermore these medicines are contraindicated in any pre-existing medical conditions with which a beta-mimetic would have an untoward effect e.g., pulmonary hypertension and cardiac disorders such as hypertrophic obstructive cardiomyopathy or any type of obstruction of the left ventricular outflow tract, e.g. aortic stenosis.

Section 4.4 – Special warnings and precautions of use

The need for cardiovascular monitoring, including ECG, of the patient throughout is also emphasised in this section in the case of tocolysis. Fluid monitoring and electrolyte balance is recommended to avoid pulmonary oedema. Blood pressure and heart rate as well blood glucose should be monitored during the administration.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

The co-administration with halogenated anaesthetics is highlighted owing to the additional antihypertensive effect and the increased uterine inertia with risk of haemorrhage. Treatment should be discontinued, whenever possible, at least 6 hours before any scheduled anaesthesia with halogenated anaesthetics.

Systemic corticosteroids are frequently given during premature labour to enhance foetal lung development. There have been reports of pulmonary oedema in women concomitantly administered with beta-agonists and corticosteroids.

Corticosteroids are known to increase blood glucose and can deplete serum potassium, therefore concomitant administration should be undertaken with caution with continuous patient monitoring owing to the increased risk of hyperglycaemia and hypokalaemia.

As the administration of beta-agonists is associated with a rise of blood glucose, individual anti-diabetic therapy may need to be adjusted.

Owing to the hypokalaemic effect of beta-agonists, concurrent administration of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, digoxin, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia.

Section 4.8 – Undesirable effects

This section has been updated with the information on cardiovascular disorders (palpitations, cardiac arrhythmias etc.), metabolic disorders (hypokalaemia, hyperglycaemia), vascular (hypotension peripheral vasodilatation) and respiratory disorders (pulmonary oedema).

Package Leaflet

The corresponding sections of the package leaflet were amended accordingly.

3. Overall discussion and benefit/risk assessment

The PRAC concluded that the benefit-risk balance of the parenteral SABAs (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) containing medicinal products in the obstetric indications is favourable as the benefits continue to outweigh the risks.

For these obstetric indications which include short term management of uncomplicated tocolysis, ECV and emergency use, 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. 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. The committee also stressed that in the patients receiving these parenteral medicinal SABA products the blood pressure and heart rate, electrolyte and fluid balance, glucose and lactate levels and potassium levels should be continuously monitored.

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 very limited efficacy data, the PRAC concluded that the benefit-risk balance is not favourable and therefore these medicinal products should no longer be indicated in any obstetric 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.

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.

4. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to inform prescribers of the deletion of the obstetric indications of the oral formulations and suppository. In addition the information on short term use (up to 48h) of the parenteral formulations and their administration under specialist supervision was highlighted. The specialists targeted are obstetricians, gynaecologists, midwives and hospital pharmacies. The communication is to be sent in accordance with the agreed communication plan. The final version of this DHPC agreed by the PRAC is provided together with the communication plan (see attachment to this report).

5. Conclusion and grounds for the 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 treatment of 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 that in accordance with Article 116 of Directive 2001/83/EC 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 the risk minimisation measures.