Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflets

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

A. Oral formulation medicinal products and suppositories

[All oral formulations and suppositories (see Annex I) should delete the obstetric indications from their product information.

In addition, any reference to the obstetric indications in all other sections of the Product information, for example in section 4.2 "Posology and methods of administration" of the Summary of Product characteristics, as well as any reference to the obstetric indications in the Package Leaflet should be removed]

B. Parenteral medicinal products for obstetric indications

[The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

I. Summary of Product Characteristics

4.1 Therapeutic indications

[The currently approved obstetric indications should be deleted and replaced by the following:]

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 following obstetric indications to be retained only where currently authorised]

External cephalic version *[to be retained only where currently authorised]*

Emergency use in specified conditions *[to be retained only where currently authorised]*

4.2 Posology and method of administration

[The wording below should be inserted in this section]

[…]

In the short term management of uncomplicated premature labour.

Treatment with <*invented name*> should only be initiated by obstetricians/physicians experienced in the use of tocolytic agents. 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; no statistically significant effect on perinatal mortality or morbidity has been observed in randomised, controlled trials. This short term delay may be used to implement other measures known to improve perinatal health.

<*invented name*> 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 of <INN SABA> (see section 4.3). This should include an adequate assessment of the patient's cardiovascular status with supervision of cardiorespiratory function and ECG monitoring throughout treatment (see section 4.4).

[Details on dose and infusion rate will need to be adapted to specifics for individual drug substances i.e. retained as is per product any reference to continuing treatment with oral maintenance therapy should be removed.]

Special cautions for infusion: 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.

Careful control of the level of hydration is essential to avoid the risk of maternal pulmonary oedema

(see section 4.4). The volume of fluid in which the drug is administered should thus be kept to a minimum. A controlled infusion device should be used, preferably a syringe pump.

[…]

4.3 Contraindications

[The wording below should be inserted in this section]

[…]

<*invented name*> is contra-indicated in the following conditions:

- Any condition at a gestational age < 22 weeks
- as a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.
- threatened abortion during the 1st and 2nd trimester
- 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.
- intrauterine foetal death, known lethal congenital or lethal chromosomal malformation.

<*invented name*> is also 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.

[…]

4.4 Special warnings and precautions for use

[The wording below should be inserted in this section]

[…]

Tocolysis

Any decision to initiate therapy with <*invented name*> should be undertaken after careful consideration of the risks and benefits of treatment.

Treatment should only be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetal health status. Tocolysis with beta-agonists is not recommended when membranes have ruptured or the cervix dilation is beyond 4cm.

<*invented name*> should be used with caution in *tocolysis* and supervision of cardiorespiratory function and ECG monitoring, should be performed throughout treatment.

The following monitoring measures must be constantly applied to the mother and, when feasible/appropriate, to the foetus:

- blood pressure and heart rate
- ECG
- electrolyte and fluid balance – to monitor for pulmonary oedema
- glucose and lactate levels – with particular regard to diabetic patients
- potassium levels– beta-agonists are associated with a decrease in serum potassium which increases the risk of arrhythmias (see section 4.5)

Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop.

<invented name> should not be used as a tocolytic agent in patients with significant risk factors for, or a suspicion of any kind of pre-existing heart disease (e.g. tachyarrhythmias, heart failure, or valvular heart disease; see section 4.3). In premature labour in a patient with known or suspected cardiac disease, a physician experienced in cardiology should assess the suitability of treatment before intravenous infusion with *<invented name>*.

Pulmonary oedema

As maternal pulmonary oedema and myocardial ischaemia have been reported during or following treatment of premature labour with beta-agonists, careful attention should be given to fluid balance and cardio-respiratory function. Patients with predisposing factors including multiple pregnancies, fluid overload, maternal infection and pre-eclampsia may have an increased risk of developing pulmonary oedema. Administration with a syringe pump as opposed to i.v. infusion will limit risk of fluid overload. If signs of pulmonary oedema or myocardial ischaemia develop, discontinuation of treatment should be considered (see section 4.2 and 4.8).

Blood pressure and heart rate

Increases in maternal heart rate of the order of 20 to 50 beats per minute usually accompany infusion of beta-agonists. The maternal pulse rate should be monitored and the need to control such increases by dose reduction or drug withdrawal should be evaluated on a case by case basis. Generally maternal pulse rate should not be allowed to exceed a steady rate of 120 beats per minute.
Maternal blood pressure may fall slightly during the infusion; the effect being greater on diastolic than on systolic pressure. Falls in diastolic pressure are usually within the range of 10 to 20mmHg. The effect of infusion on foetal heart rate is less marked, but increases of up to 20 beats per minute may occur.
In order to minimise the risk of hypotension associated with tocolytic therapy, special care should be taken to avoid caval compression by keeping the patient in the left or right lateral positions throughout the infusion.

Diabetes

Administration of beta agonists is associated with a rise of blood glucose. Therefore blood glucose and lactate levels should be monitored in mothers with diabetes and diabetic treatment adjusted accordingly to meet the needs of the diabetic mother during tocolysis (see section 4.5).

Hyperthyroidism

<invented name> should only be administered cautiously to patients suffering from thyrotoxicosis after careful evaluation of the benefits and risks of treatment.

[…]

4.5 Interaction with other medicinal products and other forms of interaction

[The wording below should be inserted in this section]

[…]

Halogenated anaesthetics

Owing to the additional antihypertensive effect, there is increased uterine inertia with risk of haemorrhage; in addition, serious ventricular rhythm disorders due to increased cardiac reactivity, have been reported on interaction with halogenated anaesthetics. Treatment should be discontinued, whenever possible, at least 6 hours before any scheduled anaesthesia with halogenated anaesthetics.

Corticosteroids

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 (see section 4.4).

Anti-diabetics

The administration of beta-agonists is associated with a rise of blood glucose, which can be interpreted as an attenuation of anti-diabetic therapy; therefore individual anti-diabetic therapy may need to be adjusted (see section 4.4).

Potassium depleting agents

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 (see section 4.4).

[…]

4.8 Undesirable effects

[The wording below should be inserted in this section]

[…]

The most common undesirable effects of <*invented name*> are correlated with the betamimetic pharmacological activity and may be limited or avoided by a close monitoring of hemodynamic parameters, such as blood pressure and heart rate, and an appropriate adjustment of the dose. They normally recede upon therapy discontinuation.

Cardiac disorders

Very common:	*Tachycardia.
Common:	*Palpitations, *decrease in diastolic pressure
Rare:	*Cardiac arrhythmias, e.g. atrial fibrillation, Myocardial ischaemia (see section 4.4)

Metabolism and nutrition disorders

Common - *Hypokalaemia
Rare - *Hyperglycaemia

Vascular disorders

Common:	*Hypotension (see section 4.4)
Rare:	*Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders

Uncommon:	*Pulmonary oedema.

* These reactions have been reported in association with the use of short acting beta-agonists in obstetric indications and are considered class effects (see section 4.4)

[…]

II. Package Leaflet

Section 1.

What <invented name> is and what it is used for.

[This section should replace any existing one which reflects the obstetric indications and should read as follows:]

- <invented name> is <also> used in women who have unexpectedly gone into early labour (premature labour) between the 22nd and 37th week of gestation, to provide a short delay in the early delivery of the baby. You will receive <invented name> for a maximum of 48 hours. This will give your doctor or midwife time to take extra measures that will improve the health of your baby.

Section 2.

[The wording below should be inserted in the relevant sections]

[…]

Before you have <invented name>

Do not have <invented name> if:

- you are less than 22 weeks pregnant
- If you suffer from or have a known risk of developing ischaemic heart disease (disease characterized by reduced blood supply to your heart muscle, causing symptoms such as chest pain (angina))
- If you have ever experienced miscarriage in the first two trimesters of your pregnancy.
- If you are pregnant and you or your baby have certain conditions when prolongation of your pregnancy would be dangerous (such as severe high blood pressure, infection of the womb, bleeding, placenta is covering the birth canal or is detaching, or your baby has died inside the womb)
- If you suffer from heart disease with palpitations (for example heart valve disorder) or long-standing lung disease (for example chronic bronchitis, emphysema) causing an increase of blood pressure to your lungs (pulmonary hypertension)

Take special care with <invented name>:

It is important to check with your doctor or nurse before having your injection if:

- you have had problems with your pregnancy,
- if during pregnancy, your waters have broken.
- you have too much fluid in the lungs causing breathlessness (pulmonary oedema)
- you have high blood pressure
- you are diabetic. If so, you may need some additional blood sugar tests when you are given <invented name>.
- you have an overactive thyroid gland
- you have a history of heart disease characterised by breathlessness, palpitations or angina (see **Do not use <invented name> if)**.

Your doctor will monitor your heart and your unborn baby. Your doctor may also take blood tests to monitor for changes in your blood (see section 3).

Taking other medicines

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This includes herbal medicines. <invented name> can have an effect on the way some medicines work, and some medicines can effect how <invented name> works.

In particular tell your doctor, nurse or pharmacist if you are taking:

- medicines for an irregular or fast heartbeat (such as digoxin)
- Other beta-blocker medicines (such as atenolol or propranolol), including eye drops (such as timolol)
- Xanthine medicines (such as theophylline or aminophylline)
- steroid medicines (such as prednisolone).
- water tablets, also known as diuretics (such as frusemide)
- medicines for diabetes to reduce your blood sugar (such as insulin, metformin, of glibenclamide).

If you are scheduled for surgery with general anaesthetics your doctor will stop the administration of <invented name> 6 hours before surgery whenever possible to protect you from adverse effects (e.g. irregular heart beat or bleeding of your womb).

Section 3.

[The wording below should be inserted in the relevant sections]

[...]

How to use <invented name>

You will never be expected to give yourself this medicine. It will always be given to you by a person who is qualified to do so after careful consideration of the balance of benefits of <invented name> to your baby and the potential untoward effects the treatment may have on you.

To temporarily delay premature labour

You will be given <invented name> by a doctor where facilities are available to continually monitor your health and that of your baby throughout administration.

The following measures will be taken where necessary:

- Blood pressure and heart rate. Your doctor will consider the lowering of your dose or discontinuing <invented name> if your heart rate exceeds 120 beats per minute.
- Electrocardiography (ECG, electric activity of your heart) **Tell your doctor immediately if you experience chest pain during treatment.** If there are changes in ECG recording and you have chest pain your doctor will stop the administration of <invented name>.

- Balance of water and salts in your body. **Tell your doctor immediately if you experience coughing or shortness of breath during treatment**. If any signs indicate that there is a build-up of fluid in your lungs (also known as pulmonary oedema) (e.g. coughing or shortness of breath), your doctor may stop the administration of <invented name>.
- Blood sugar level and the occurrence of low body pH with a build-up of lactate in your blood (also known as lactic acidosis)
- Blood potassium levels (low potassium levels may be associated with a risk of irregular heart beat)

Section 4.

[The wording below should be inserted in the relevant sections]

[…]

Possible side effects

Important side effects to look out for when treated for premature labour:

Rare (affects less than 1 in 1,000 people)
Chest pain (due to heart problems such as angina). If this happens to you, tell your doctor or nurse straight away.
The following side effects have also been observed with all beta-agonists like <invented name> when used to delay premature labour.

Very common (affects more than 1 in 10 people)
- Fast heart beats

Common (affects less than 1 in 10 people)
- Pounding heart beat (palpitations),
- Low blood pressure which may cause light-headedness or dizziness
- Low levels of potassium in your blood which may cause muscle weakness, thirst, or “pins and needles”

Uncommon (affects less than 1 in 100 people)
- Fluid accumulation in the lungs (pulmonary oedema) which may cause difficulty breathing

Rare (affects less than 1 in 1,000 people)
- Unusual or irregular heartbeats
- High levels of sugar (glucose) and/or lactic acid in your blood
- Flushing (reddening) of the face