Part VI: Summary of the risk management plan

Summary of risk management plan for misoprostol

This is a summary of the risk management plan (RMP) for misoprostol. The RMP details important risks of misoprostol, how these risks can be minimised, and how more information will be obtained about misoprostol's risks and uncertainties (missing information).

misoprostol's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how misoprostol should be used.

Important new concerns or changes to the current ones will be included in updates of misoprostol's RMP.

I. The medicine and what it is used for

Misoprostol are authorised for induction of labour (IOL) - (see SmPC for the full indication). It contains misoprostol as the active substance, and it is given by oral administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of misoprostol together with measures to minimise such risks are outlined below. and the proposed studies for learning more about misoprostol's risks are planned.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of misoprostol are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important

risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of misoprostol. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	- Uterine hyperstimulation - Foetal heart rate disorder due to uterine hyperstimulation - Perinatal asphyxia due to uterine hyperstimulation - Uterine rupture
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Uterine hyperstimulation	
Evidence for linking the risk to the medicine	This safety concern is considered an identified risk as its association with misoprostol is considered proven. It is considered important as the triggered adverse effects may become life threatening if left untreated. Uterine hyperstimulation has been seen with various prostaglandin agents used for labour induction. Based on the meta-analysis performed by the applicant, when comparing with mechanical methods, a significantly increase in uterine tachysystole was found in the 25-microgram oral misoprostol group. However, at 50 micrograms, this difference was not confirmed with the rate of uterine tachysystole in favour of oral misoprostol.
Risk factors and risk groups	No risk groups or risk factors was detected for uterine hyperstimulation. The meta-analysis performed by the applicant did not evidence any clear dose-response relationship between 25 microgram and 50 micrograms on uterine hyperstimulation. The risk ratio for the uterine tachysystole rate tended to be in favour of oral misoprostol at the 25 micrograms dose, while it tended to be in favour of titrated oral misoprostol when compared to oral misoprostol at the 50 micrograms dose, although this was not statistically significant.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 4.9*

	SmPC section 4.4 where recommendation to stop administration of misoprostol is given in case of hyperstimulation. *SmPC section 4.4 and 4.2 where recommendation is given regarding administration of misoprostol to be carried out only by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring to be carried out.* *PL section 2, 3 and 4* *Section 2 and 4 where recommendation regarding stopping the treatment with misoprostol in case of hyperstimulation of the uterus and that misoprostol must be administered by trained obstetric personnel in hospital setting for monitoring of mother and the baby is provided* Additional risk minimisation measures *None*
Important identified risk: Foetal heart rate disorder due to uterine hyperstimulation	
Evidence for linking the risk to the medicine	This safety concern is considered an identified risk as its association with misoprostol is considered proven. It is considered important as the inadequate oxygen supply to the foetus can become life-threatening if left untreated. The risk of foetal heart rate disorder is related to uterine hyperstimulation as strong uterine contractions during labour can impair the maternal blood flow to the placenta and decrease oxygen delivery to the foetus [Neilson JP 2015].
Risk factors and risk groups	No risk groups or risk factors was detected for foetal heart rate disorder due to uterine hyperstimulation. The meta-analysis performed by the applicant did not evidence any clear dose-response relationship between 25 microgram and 50 micrograms on uterine hyperstimulation. The risk ratio for the uterine tachysystole rate tended to be in favour of oral misoprostol at the 25 micrograms dose, while it tended to be in favour of titrated oral misoprostol when compared to oral misoprostol at the 50 micrograms dose, although this was not statistically significant.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.4, 4.5, 4.8, 4.9* *SmPC section 4.4 where recommendation is given regarding administration of misoprostol to be carried out*

	only by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring to be carried out *SmPC section 4.4 where recommendation to stop administration of misoprostol is given in case of hyperstimulation* *PL section 2,3 and 4.* *Section 2 and 4 where recommendation regarding stopping the treatment with misoprostol in case of hyperstimulation of the uterus and that misoprostol must be administered by trained obstetric personnel in hospital setting for monitoring of mother and the baby is provided* Additional risk minimisation measures *None*
Important identified risk: Perinatal asphyxia due to uterine hyperstimulation	
Evidence for linking the risk to the medicine	This safety concern is considered an identified risk as its association with misoprostol is considered proven. It is considered important as the inadequate oxygen supply to the foetus can become life-threatening if left untreated. The risk of perinatal asphyxia is related to uterine hyperstimulation as strong uterine contractions during labour can impair the maternal blood flow to the placenta and decrease oxygen delivery to the foetus [Neilson JP 2015].
Risk factors and risk groups	No risk groups or risk factors was detected for perinatal asphyxia due to uterine hyperstimulation. The meta-analysis performed by the applicant did not evidence any clear dose-response relationship between 25 microgram and 50 micrograms on uterine hyperstimulation. The risk ratio for the uterine tachysystole rate tended to be in favour of oral misoprostol at the 25 micrograms dose, while it tended to be in favour of titrated oral misoprostol when compared to oral misoprostol at the 50 micrograms dose, although this was not statistically significant.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 4.9* *SmPC section 4.4 where recommendation is given regarding administration of misoprostol to be carried out*

	only by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring to be carried out *SmPC section 4.8 where 'Neonatal asphyxia' included as undesirable effect.* *PL section 2, 3 and 4* *Section 2 and 4 where recommendation regarding stopping the treatment with misoprostol in case of hyperstimulation of the uterus and that misoprostol must be administered by trained obstetric personnel in hospital setting for monitoring of mother and the baby is provided* Additional risk minimisation measures *None*
Important identified risk: Uterine rupture	
Evidence for linking the risk to the medicine	This safety concern is considered an identified risk as its association with misoprostol is considered proven. It is considered important as the uterine rupture can cause severe maternal haemorrhage, foetal hypoxia and the foetus can enter the abdominal cavity, necessitating urgent obstetric intervention.
Risk factors and risk groups	Induction of labour (IOL) in women with a history of caesarean section is widely recognized as an independent risk factor for uterine rupture. This risk is present regardless of the pharmacologic agent used—whether oxytocin, prostaglandin E2 (PGE2), or misoprostol—and has been estimated to range between 9 and 24.5 per 1,000 women [Bennett KA et al. 1997; Plaut MM et al. 1999]. The scar from the previous caesarean section weakens the uterine wall in the area where the incision was made. The same is also relevant for other previous uterine or cervical surgeries due to scar tissue.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.4, 4.5, 4.8, 4.9* *SmPC section 4.3 where misoprostol is contraindication in suspicion or evidence of uterine scarn resulting from previous uterine or cervical surgery.* *PL section 2, 3 and 4* *Section 4 where 'Rupture of womb' included as possible side effect* Additional risk minimisation measures *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of misoprostol.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for misoprostol.