Part VI: Summary of the risk management plan

Summary of risk management plan for Angusta (misoprostol)

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

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

I. The medicine and what it is used for

Angusta is authorised for the induction of labour. It contains misoprostol as the active substance and it is given orally by 25µg tablets.

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

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

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.

If important information that may affect the safe use of Angusta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Angusta 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 Angusta. 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	From the Cochrane review concerning oral misoprostol for induction of labour[9], in studies where most women were given 20 µg two-hourly, the hyperstimulation rates were the same as for vaginal dinoprostone (i.e. around 5% overall; 3.5% had foetal heart rate (FHR) abnormalities). From the ICSR information available cumulatively, there have been 30 reports of uterine hyperstimulation in the Global Safety Database. Of the 30 reports, event outcome was reported as: recovered/resolved [27], recovering/resolving [2] and not recovered/resolved [1]. In the compassionate use programme, 20 case reports (all serious) were reported.
Risk factors and risk groups	The risk of uterine hyperstimulation is related to dose. There are studies showing a trend towards higher C_{max}, AUC and $t_{½}$ of misoprostol in patients with renal or hepatic impairment.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 contraindicates use of Angusta when oxytocic drugs and/or other labour induction agents are being given. SmPC section 4.4 states Angusta can cause excessive uterine stimulation and recommends if uterine contractions are prolonged or excessive then additional tablets should not be administered and treatment according to local guidelines should be started.

	SmPC section 4.9 states in cases of overdose symptoms, dosing with Angusta should be stopped and treatment according to local guidelines should be started. Caesarean section should be considered in cases of uterine hyperstimulation where there is potential for foetal heart rate disorders and asphyxia. SmPC sections 4.2 and 4.4 state Angusta should only be administered by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring should be available. SmPC section 4.8 states uterine hyperstimulation is a listed event with a frequency of common (≥ 1/100 to < 1/10). PL section 2 states do not take Angusta if oxytocic drugs and/or other labour induction agents are being given. Angusta can cause excessive stimulation of the womb. If contractions are prolonged or too strong the patient will not be given any more tablets and the doctor or midwife will decide if further treatment is required. The section also states that the product must only be given by a trained professional in a hospital where facilities for monitoring the patient and baby are available. PL section 3 states the midwife or doctor will stop Angusta if the contractions are too strong or last too long and in cases of overdose. The midwife or doctor will decide if any medicines should be given to reduce or slow down contractions. PL section 4 states uterine hyperstimulation is a common side effect (may effect up to 1 in 10 people). **Additional risk minimisation measures:** None

Important identified risk: Foetal heart rate disorder due to uterine hyperstimulation	
Evidence for linking the risk to the medicine	From the Cochrane review concerning oral misoprostol for induction of labour[9], in studies where most women were given 20 µg two-hourly, the hyperstimulation rates were the same as for vaginal dinoprostone (i.e. around 5% overall; 3.5% had FHR abnormalities). From the ICSR information available cumulatively, there have been 12 reports of foetal heart rate disorder in the Global Safety Database. Of the 12 reports, event outcome was reported as: recovered/resolved [9], unknown [2] and fatal [1]. Following the DLP of this

	RMP, one further report of foetal heart rate disorder has been received for which the patient outcome was not reported. In the compassionate use programme, 16 case reports (14 serious) were reported.
Risk factors and risk groups	The risk of foetal heart rate disorder due to uterine hyperstimulation is related to dose. The mother is additionally at risk for uterine hyperstimulation.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 contraindicates use of Angusta when oxytocic drugs and/or other labour induction agents are being given. SmPC section 4.4 states Angusta can cause excessive uterine stimulation and recommends if uterine contractions are prolonged or excessive then additional tablets should not be administered and treatment according to local guidelines should be started. SmPC section 4.9 states in cases of overdose symptoms, dosing with Angusta should be stopped and treatment according to local guidelines should be started. Caesarean section should be considered in cases of uterine hyperstimulation where there is potential for foetal heart rate disorders and asphyxia. SmPC sections 4.2 and 4.4 state Angusta should only be administered by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring should be available. SmPC section 4.8 states uterine hyperstimulation is a listed event with a frequency of common (≥ 1/100 to < 1/10). Abnormal foetal heart rhythm is a listed event with a frequency of common (≥ 1/100 to < 1/10) at 50 micrograms every four hours, and a frequency of uncommon (≥ 1/1,000 to < 1/100) at 25 micrograms every 2 hours. PL section 2 states do not take Angusta if oxytocic drugs and/or other labour induction agents are being given. Angusta can cause excessive stimulation of the womb. If contractions are prolonged or too strong the patient will not be given any more tablets and the doctor or midwife will decide if further treatment is required. The section also states that the product must only be given by a trained professional in a

	hospital where facilities for monitoring the patient and baby are available. PL section 3 states the midwife or doctor will stop Angusta if the contractions are too strong or last too long and in cases of overdose. The midwife or doctor will decide if any medicines should be given to reduce or slow down contractions. PL section 4 states uterine hyperstimulation and foetal heart rate abnormal are common side effects (may effect up to 1 in 10 people). (Foetal heart rate abnormal is reported as common for 50 µg every 4 hours). Foetal heart rate abnormal is also mentioned as an Uncommon Side effect (may affect up to 1 in 100 people) for 25 µg every 2 hours. **Additional risk minimisation measures:** None

Important identified risk: Perinatal asphyxia due to uterine hyperstimulation	
Evidence for linking the risk to the medicine	No data concerning perinatal asphyxia due to uterine hyperstimulation was available from the Cochrane review concerning oral misoprostol for induction of labour[9]. From the ICSR information available cumulatively, there have been nine reports of perinatal asphyxia in the Global Safety Database. Of the nine reports, event outcome was reported as: recovered/resolved [7], fatal [1] and unknown [1]. In the compassionate use programme four case reports (all serious) were reported.
Risk factors and risk groups	The risk of foetal asphyxia due to uterine hyperstimulation is related to dose. The mother is additionally at risk for uterine hyperstimulation.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 contraindicates use of Angusta when there is suspicion or evidence of foetal compromise or when there is foetal malpresentation, contradicting vaginal delivery. This section also contraindicates use of Angusta when oxytocic drugs and/or other labour induction agents are being given.

	SmPC sections 4.2 and 4.4 state Angusta should only be administered by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring should be available. SmPC section 4.8 states uterine hyperstimulation is a listed event with a frequency of common (≥ 1/100 to < 1/10), and neonatal asphyxia is a listed with a frequency of not known. SmPC section 4.9 states in cases of overdose symptoms, dosing with Angusta should be stopped and treatment according to local guidelines should be started. Caesarean section should be considered in cases of uterine hyperstimulation where there is potential for foetal heart rate disorders and asphyxia. PL section 2 states do not take Angusta if oxytocic drugs and/or other labour induction agents are being given, if the midwife or doctor considers the baby to not be in good health or is distressed, if there is foetal malpresentation or if there's any womb abnormalities that would prevent a vaginal delivery. Angusta can cause excessive stimulation of the womb. If contractions are prolonged or too strong the patient will not be given any more tablets and the doctor or midwife will decide if further treatment is required. The section also states that the product must only be given by a trained professional in a hospital where facilities for monitoring the patient and baby are available. PL section 3 states the midwife or doctor will stop Angusta if the contractions are too strong or last too long and in cases of overdose. The midwife or doctor will decide if any medicines should be given to reduce or slow down contractions. PL section 4 states uterine hyperstimulation is a common side effect (may effect up to 1 in 10 people) and neonatal asphyxia is a side effect, however the frequency is not known. **Additional risk minimisation measures:** None

Important identified risk: Uterine rupture	
Evidence for linking the risk to the medicine	From the Cochrane review concerning oral misoprostol for induction of labour[9] it was reported: "some observational studies have reported a high uterine

	rupture rate when vaginal misoprostol was given to women who have had previous caesarean sections. There is less evidence for oral misoprostol, but there were rupture rates of 10% (one of 10 women) and 9.7% (four of 41 women) in two studies that used oral misoprostol for induction[10,11]." In the Aslan study[11], women who underwent induction of labour with misoprostol and with a history of caesarean delivery were retrospectively compared with those without uterine scarring. The rate of uterine rupture (9.7%) was significantly higher in patients with a previous caesarean delivery (P<0.001). No uterine rupture occurred in 50 patients without uterine scarring. From the ICSR information available cumulatively, there have been five reports of uterine rupture in the Global Safety Database. Of the five reports, event outcome was reported as: recovered/resolved [3], recovered/resolved with sequelae [1] and unknown [1]. Following the DLP of this RMP, four further reports of uterine rupture have been received, for which the patient outcomes were reported as: recovered with sequelae [2], unknown [1] and not reported [1]. In the compassionate use programme no case reports concerning uterine rupture were reported.
Risk factors and risk groups	The use of misoprostol in women with prior caesarean section or major uterine surgery has been associated with an increased risk of uterine rupture and, therefore, should be avoided. Other predisposing factors include congenital uterine abnormalities and trauma[15].
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 contraindicates use of Angusta in case of suspicion or detection of uterine scarring as a result of previous surgical procedures in the uterus or cervix, e.g. caesarean section. SmPC sections 4.2 and 4.4, and PL sections 2 and 3 state Angusta should only be administered by trained obstetric personnel in a hospital setting and continuous foetal and uterine monitoring should be available. SmPC section 4.8 states uterine rupture is a listed event with a frequency of not known.

	PL section 2 states do not take Angusta if the patient has had previous cervix or womb surgery including previous caesarean section. PL section 4 states uterine rupture is a side effect with frequency of not known. **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 Angusta.

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

There are no studies required for Angusta.