SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Angusta 25 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 micrograms misoprostol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, uncoated oval shaped tablets with the dimensions 7.5 x 4.5 mm with a score line on one side and plain on the other. The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Angusta is indicated for induction of labour.

4.2 Posology and method of administration

Posology
The recommended dosing regimen for Angusta is 25 micrograms orally every two hours or 50 micrograms orally every four hours according to hospital practice. The maximum dose is 200 micrograms over a period of 24 hours.

There may be a synergistic/additive effect of misoprostol and oxytocin. Plasma concentrations of misoprostol acid are negligible after 5 half-lives (3.75 hours), see section 5.2. It is recommended to wait 4 hours after the last dose of Angusta before administration of oxytocin (see sections 4.3, 4.4 and 4.5).

Due to the lack of clinical data, the use of Angusta is recommended from 37th week of pregnancy when the cervix is unfavourable (Bishop score <7).

Special populations
A lower dose and/or prolonged dosing intervals should be considered in pregnant women with renal or hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Angusta in pregnant women aged less than 18 years has not been established in clinical trials. No data are available.

Method of administration

- Angusta should only be administered by trained obstetric personnel in a hospital setting where facilities for continuous fetal and uterine monitoring is available.
- The cervix should be assessed carefully before Angusta is administered.
- Angusta should be taken orally with a glass of water.

4.3 Contraindications

Angusta is contraindicated:

- When there is hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- When labour has started
- When there is suspicion or evidence of foetal compromise prior to induction (e.g., failed non-stress or stress test, meconium staining or diagnosis or history of non-reassuring foetal status)
- When oxytocic drugs and/or other labour induction agents are being given (see section 4.2, 4.4, 4.5 and 5.2)
- When there is suspicion or evidence of uterine scar resulting from previous uterine or cervical surgery, e.g. caesarean delivery
- When there is uterine abnormality (e.g. bicornuate uterus) preventing vaginal delivery
- When there is placenta praevia or unexplained vaginal bleeding after 24 weeks gestation with this pregnancy
- When there is foetal malpresentation, contraindicating vaginal delivery
- In patients with kidney failure (GFR <15 ml/min/1.73 m^2).

4.4 Special warnings and precautions for use

Angusta should only be administered by trained obstetric personnel in a hospital setting where facilities for continuous fetal and uterine monitoring is available and the cervix should be assessed carefully before product use.

Angusta can cause excessive uterine stimulation.

If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, additional Angusta tablets should not be administered. If excessive uterine contractions continue, treatment according to local guidelines should be started.

In women with pre-eclampsia, evidence or suspicion of foetal compromise should be ruled out (refer to section 4.3). There are no or limited clinical data with misoprostol in pregnant women with severe pre-eclampsia marked by Haemolytic anaemia; Elevated Liver enzymes;

Low Platelet count (HELLP) syndrome, other end organ affliction or CNS findings other than mild headache.

Chorioamnionitis may necessitate fast delivery. Decisions regarding antibiotic treatment, induced labour or caesarean section will be at the physician's discretion.

There are no or limited clinical data with misoprostol in women whose membranes have been ruptured for more than 48 hours prior to administration of misoprostol.

There may be synergistic/additive effects of misoprostol and oxytocin. Concomitant administration of oxytocin is contraindicated. See section 4.3. Angusta is eliminated after 4 hours. See section 5.2. It is recommended to wait 4 hours after last dose of Angusta before administration of oxytocin (see sections 4.2 and 4.5).

There are no or limited clinical data with misoprostol in multiple pregnancies. There are no or limited clinical data with misoprostol in grand multiparity.

There are no or limited clinical data with misoprostol before week 37 of gestation (see section 4.6).

Angusta should be used only when induction of labour is clinically indicated.

There are no or limited clinical data with misoprostol in pregnant women with Bishop score (mBS) >6.

An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour has been induced by any physiological or pharmacological method.

A lower dose and/or prolonged dosing intervals should be considered in pregnant women with renal or hepatic impairment (see section 5.2).

This medicinal product contains 0,874 mg sodium per tablet that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Angusta.

Concurrent use of oxytocic drugs or other labour induction agents is contraindicated due to the potential of increased uterotonic effects (see sections 4.2, 4.3, 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

Angusta has been studied in pregnant women ≥37 weeks of gestation.
Angusta should only be used prior to 37 weeks of gestation if medically indicated (see section 4.4).

Angusta is used for labour induction at a low misoprostol dosage for a short period of time at the very end of pregnancy. When used at that time of pregnancy, there is no risk of foetal malformations. Angusta should not be used at any other time during pregnancy: a threefold increased risk of foetal malformations (including Moebius syndrome, amniotic band syndrome and central nervous system anomalies) has been reported in pregnancies exposed to misoprostol in first trimester.

Breast-feeding
No studies have been performed to investigate the amount of misoprostol acid in colostrum or breast milk following the use of Angusta.

Misoprostol has been detected in human milk following oral administration of misoprostol in tablet form.

Pharmacokinetic trials reveal that oral misoprostol (at dose levels of 600 µg and 200 µg) is excreted into breast milk with drug levels that rise and fall very quickly. The maximum concentration of misoprostol acid in expressed breast milk was achieved within 1 hour after dosing and was 7.6 pg/ml (% CV 37%) and 20.9 pg/ml (% CV 62%) after single 200 mcg and 600 mcg misoprostol administration, respectively. Negligible amounts of misoprostol acid remain in maternal plasma after 5 half-lives (3.75 hours), and even lower concentrations will remain in breast milk. Breast-feeding can start 4 hours after the last dose of Angusta is administered.

Fertility
Studies of fertility and embryo development in rats have shown that misoprostol may have an impact on implantation and resorption. This is, however, considered of no relevance for the indicated use of Angusta in late pregnancy.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The undesirable effects listed in the table below have been reported in 41 trials where a total of 3,152 women were exposed to oral misoprostol at doses of 20-25 µg every 2 hours or 50 µg every 4 hours. In addition, adverse events reported in a compassionate use program, where approximately 29,000 women have been exposed to Angusta for induction of labour are also listed.

System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Not known (cannot be estimated from the available data)** [1)]
Nervous system disorders				Dizziness Convulsion neonatal*
Respiratory, thoracic and mediastinal disorders				Neonatal asphyxia* Cyanosis neonatal*
Gastrointestinal disorders	*With 50 µg, 4-hourly:* Nausea[2)] Vomiting[3)]	Diarrhoea *With 25 µg, 2-hourly:* Nausea[2)] Vomiting[3)]		

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not known (cannot be estimated from the available data) [1)]
Skin and subcutaneous tissue disorders				Rash pruritic
Pregnancy, puerperium and perinatal conditions	Meconium stain *With 25 µg, 2-hourly:* Postpartum haemorrhage[5)]	Uterine hyperstimulation[4)] *With 50 µg, 4-hourly:* Postpartum haemorrhage[5)]		Foetal acidosis* Premature separation of placenta Uterine rupture
General disorders and administration site conditions		Chills Pyrexia		
Investigations		*With 50 µg, 4-hourly:* Apgar score low*[6)] Foetal heart rate abnormal*[7)]	*With 25 µg, 2-hourly:* Apgar score low*[6)] Foetal heart rate abnormal*[7)]	

* Neonatal adverse reaction

1) ADRs which were reported from the compassionate use programme including birth hospitals in Denmark, Norway and Finland, where approximately 29,000 women have been exposed to Angusta for induction of labour.
2) Nausea was common with 25 µg every 2 hours and very common with 50 µg every 4 hours.
3) Vomiting was common with 25 µg every 2 hours and very common with 50 µg every 4 hours.
4) Uterine hyperstimulation was reported both with and without foetal heart rate changes.
5) Postpartum haemorrhage was very common with 25 µg every 2 hours and common with 50 µg every 4 hours.
6) Apgar score low was uncommon with 25 µg every 2 hours and common with 50 µg every 4 hours.
7) Foetal heart rate abnormal was reported in connection with uterine hyperstimulation.
Uterine hyperstimulation with foetal heart rate changes was uncommon with 25 µg every 2 hours and common with 50 µg every 4 hours.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple Store.

4.9 Overdose

There is no information on overdose with Angusta.
In case of overdose symptoms (e.g. excessive uterine stimulation causing prolonged or excessive contractions), dosing with Angusta should be arrested and treatment according to local guidelines should be started. The potential consequences of uterine hyperstimulation include foetal heart rate disorders and asphyxia in which case caesarean section should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynaecologicals, oxytocics, prostaglandins, ATC-code: G02AD06

Mechanism of action

Misoprostol is a synthetic analogue of Prostaglandin E1 (PGE1), a naturally occurring oxytocic compound. Prostaglandins of the F and E series have been shown to increase collagenase activity in rabbit uterine cervix fibroblasts in vitro and to cause cervical ripening and uterine contraction in vivo. These pharmacodynamic effects are considered to be the mechanism of action relevant for the clinical effect of Angusta

PGE analogues also have a number of other effects, e.g. relaxation of bronchial and tracheal muscles, increase of mucus secretion and decrease of acid and pepsin secretion in the stomach, increase of renal blood flow, increase of circulating concentrations of adrenocorticotropic hormone and prolactin. These pharmacodynamic effects are considered to be of no clinical importance with the short treatment.

Clinical efficacy and safety

Posology 25 µg 2-hourly

Knowledge about efficacy and safety is based on meta-analyses of 4 clinical studies where 637 women were exposed to the dosing regimen, oral misoprostol 20-25 µg 2-hourly.

Comparator	**Number of studies**	**Exposure to oral misoprostol 20 or 25 µg 2-hourly**
Oxytocin	2	169 women
Dinoprostone[1)]	2 (one double-blind)	468 women (365 in double-blind study)

1) Dinoprostone administered vaginally

In three of the trials (596 women), the main inclusion criterion was term pregnancy. For one trial (41 women), the main inclusion criterion was term pregnancy and Prelabour Rupture of Membranes (PROM). The double-blind trial, Dodd 2006 is considered pivotal and is described in detail in the following.

Dodd 2006 was a randomised double-blind, double-dummy, active-controlled (vaginal dinoprostone gel) study (N=365/376). Women at term pregnancy (> 36 weeks + 6 days) with singleton pregnancies in cephalic presentation without complications and Bishop score <7 were eligible. The primary endpoints were vaginal delivery not achieved within 24 hours, uterine hyperstimulation with fetal heart rate change (FHR) and caesarean sections.

There was no statistically significant difference between oral misoprostol and vaginal dinoprostone with regards to vaginal delivery not achieved within 24 hours (oral misoprostol 168/365 (46.0%) v dinoprostone 155/376 (41.2%); relative risk 1.12, 95% confidence interval 0.95 to 1.32; P = 0.134).

There was a lower (not statistically significant) risk in the oral misoprostol group for uterine hyperstimulation with fetal heart rate changes, caesarean section and low Apgar score. There was a statistically significant lower risk of uterine hyperstimulation without fetal heart rate changes in women treated with oral misoprostol. There was no difference in the secondary outcomes such as neonatal cord pH and blood loss.

Posology 50 µg 4-hourly

Knowledge about efficacy and safety is based on meta-analyses of 23 clinical trials where 2,515 women were exposed to the dosing regimen, oral misoprostol 50 µg 4-hourly.

Comparator	**Number of studies**	**Exposure to oral misoprostol 50 µg 4-hourly**
Placebo	3 (two double-blind)	247 women (97 in double-blind studies)
Oxytocin	2	91 women
Dinoprostone[1)]	3	155 women
Vaginal misoprostol	10 (three double-blind)	867 women (215 in double-blind studies)
Other comparators[2)]	5 (one double-blind)	1155 women (32 in double-blind study)

1) Dinoprostone administered vaginally or intracervically
2) Titrated oral misoprostol, higher dose oral misoprostol, combinations of oxytocin and PGE gel and Foley Catheter

The main inclusion criterion in all three placebo controlled trials was PROM.

In one study comparing against oxytocin, the main inclusion criterion was PROM (55 women) and in the other study the main inclusion criterion was term pregnancy (36 women).

All three studies comparing against dinoprostone (administered vaginally or intracervically) were open label studies. In one study, the main inclusion criterion was PROM (31 patients) whereas the main inclusion criterion was term pregnancy (124 women) for the other two studies.

Three of the studies comparing against vaginal misoprostol were double blind studies (215 women were exposed). In one double-blind study, the main inclusion criterion was PROM (51 women). In the two other double-blind studies, the main inclusion criterion was term pregnancy (164 women). The remaining seven studies were open label studies with the main inclusion criterion being term pregnancy (652 women).

An additional 5 studies (1155 women) compared to various comparators such as titrated misoprostol, higher dose misoprostol, combinations of oxytocin and PGE gel; and Foley Catheter. These trials are supportive for safety, only.

The double-blind trials Bennett 1998 and Levy 2007 are considered pivotal and are described in detail in the following.

Bennett 1998 was a randomized double-blind active controlled (vaginal misoprostol) study (N=104/102) comparing oral to vaginal use of 50 µg of misoprostol administered every 4 hours in women at term with intact membranes. The study stratified for low (<7) or high (≥7) Bishop score. The primary endpoint was time from induction to vaginal birth. Other endpoints were frequency of excessive uterine activity resulting in abnormal fetal heart rate (FHR), neonatal morbidity (as measured by cord blood acid-base analysis and ACOG criteria for birth asphyxia), caesarean birth, maternal gastrointestinal side effects, and patient satisfaction.

Time from induction to delivery was statistically significantly shorter with vaginal misoprostol than with oral misoprostol (14.1 hours vs 17.9 hours, p=0.004).

For other outcomes, such as risk of uterine hyperstimulation with fetal heart rate changes and caesarean section, there was a lower (not statistically significant) risk in the oral misoprostol group. There was a statistically significantly lower risk of uterine hyperstimulation without fetal heart rate changes in the oral misoprostol group.

Levy 2007 was a double-blind study (N=64/66) investigating the 50 µg 4-hourly posology against placebo in women with prelabour rupture of membranes (PROM). The primary endpoint was delivery within 24 hours from PROM.

The time to delivery was statistically significantly shortened with oral misoprostol compared to placebo with only a slight (not statistically significant) increase in the frequency of uterine hyperstimulation. For other safety outcomes, such as risk of caesarean section, there appeared to be a lower risk in the oral misoprostol group (not statistically significant). No neonates had an Apgar score less than 7 at 5 min.

The clinical study (AZ-201) supports the safety and efficacy of Angusta for induction of labour.

Paediatric population

The European Medicines Agency has waived the obligation to submit results of clinical studies with Angusta in all subsets of the paediatric population in labour induction, in the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Misoprostol, an ester, is rapidly metabolised to its active metabolite misoprostol acid. Only misoprostol acid is detectable in plasma. The acid is further metabolised by beta fatty acid oxidation to inactive dinor and tetranor acid metabolites prior to excretion in the urine.

After oral administration of Angusta, misoprostol is rapidly absorbed, with peak plasma levels of the active metabolite (misoprostol acid) occurring after

approximately 30 minutes. The mean plasma elimination half-life of misoprostol acid is approximately 45 minutes.

The dose normalized AUC following 25 and 50 µg misoprostol (Angusta) were not statistically significantly different. Mean±SD were 107.8±53.16 and 128.1±45.60 h·pg/ml, respectively.

The serum protein binding of misoprostol acid is less than 90% and concentration independent at therapeutic doses.

Administration of misoprostol with food does not change the bioavailability of misoprostol acid, but reduces the maximum plasma concentration due to a slower absorption rate.

There are studies showing a trend towards higher C_{max}, AUC and $t_{½}$ in patients with renal or hepatic impairment. See sections 4.2, 4.3 and 4.4

5.3 Preclinical safety data

Published literature on misoprostol studies of safety pharmacology, acute and repeated dose toxicity, mutagenicity, carcinogenicity and reproductive toxicity reveals no special hazard for humans.

In humans, misoprostol exposure in early pregnancy (failed, early medication pregnancy termination) has been associated with multiple congenital defects. Since teratogenicity studies do not confirm direct teratogenic effects of misoprostol, these malformations are thought to be due to vascular disruption and disturbed blood supply to the developing embryo secondary to uterine contractions caused by misoprostol administered for medication pregnancy termination.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Cellulose, microcrystalline
Maize starch

Crospovidone

Croscarmellose sodium
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Angusta is available in a pack of double layer aluminium foil blister containing 8 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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