Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gyxiny 25 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 microgram misoprostol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, 4.5 mm round, flat, rounded edge tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Gyxiny is indicated for induction of labour.

4.2 Posology and method of administration

Posology
The recommended dosing regimen for Gyxiny is 25 microgram orally every two hours or 50 microgram orally every four hours according to hospital practice/local guidelines for management of induction of labour. The maximum daily dose is 200 microgram.

The use of this medicinal product is recommended from week 37 of pregnancy when the cervix is unfavourable (Bishop score <7).

Special populations
Lower dose and/or prolonged dosing intervals should be considered in pregnant women with renal or hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of this medicinal product in pregnant women aged less than 18 years have not been established. No data are available.

Method of administration

- Treatment 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 this medicinal product is administered.
- Tablets should be taken orally with a glass of water.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to other prostaglandins.
- When labour has started.
- When there is suspicion or known evidence of fetal compromise.
- When oxytocin and/or other labour induction agents are being given (see sections 4.4 and 4.5)
- When there is suspicion or evidence of uterine scar resulting from previous uterine or cervical surgery, e.g., caesarean section.

- When vaginal delivery is contraindicated.
- When there is placenta praevia or unexplained vaginal bleeding after 24 weeks gestation.
- When there is a kidney failure with GFR <15 ml/min/1.73 m^2.

4.4 Special warnings and precautions for use

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

Misoprostol can cause hyperstimulation of the uterus. In that case or if there is a clinical concern for the mother or the baby, this medicinal product administration should be stopped, and supportive care according to local guidelines should be provided.

There may be synergistic/additive effects of misoprostol and oxytocin. Concomitant administration of oxytocin is contraindicated (see section 4.3). It is recommended to wait 4 hours after the last dose of misoprostol before administration of oxytocin.

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

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

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

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

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 less than 1 mmol sodium (23 mg) per dose, 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 misoprostol.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Misoprostol 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. this medicinal product should not be used at any other time during pregnancy: a threefold increased risk of foetal malformations (including moebious syndrome, amniotic band syndrome and central nervous system anomalies) have been reported in pregnancies exposed to misoprostol in first trimester.

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

Breast-feeding
Misoprostol has been detected in human breast milk following oral administration of misoprostol in tablet form. Pharmacokinetic studies show that peroral misoprostol (at doses 600 microgram and 200 microgram) is excreted into breast milk, with drug levels rising and falling very rapidly. The maximum concentration of misoprostol acid in breast milk was reached within 1 hour after dosing and was 7.6 picograms/ml (% CV 37%) and 20.9 picograms/ml (% CV 62%) following single administrations of 200 microgram and 600 microgram of misoprostol, respectively. The half-life in milk averaged 1.1 hours. Negligible amounts of misoprostol acid are found in maternal plasma after 5 half-lives (3.75 hours).

Based on the very low levels of misoprostol in breastmilk, amounts ingested by the infant would not be expected to cause any adverse effects in breastfed infants. Therefore, breast-feeding is possible for women who have been treated with misoprostol.

Fertility
Studies of fertility and early embryo development in rats have shown that misoprostol may have an impact on implantation and resorption (see section 5.3). This is, however, considered of no relevance for the indicated use of misoprostol in late pregnancy.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
The undesirable effects listed in the table below have been reported in 38 trials where a total of 4,403 pregnant women were exposed to oral misoprostol at doses of 20-25 microgram every 2 hours or 50 microgram every 4 hours. Safety data of oral misoprostol 20 or 25 microgram 2-hourly for induction of labour are available from meta-analysis of 11 clinical trials where 1,459 women were exposed to oral misoprostol 20 or 25 microgram 2-hourly. Safety data of oral misoprostol 50 microgram 4-hourly for induction of labour are available from meta-analysis of 28 clinical studies where 2,944 women were exposed to oral misoprostol 50 microgram 4-hourly.
Among 54 healthy women who received a single dose of 50 microgram of this medicinal product, no adverse event related to misoprostol administration was detected.

Tabulated list of adverse reactions
Adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Not known (cannot be estimated from the available data)**
Nervous system disorders				Dizziness[1)] Neonatal seizures (PT: convulsion neonatal)*[2)]
Respiratory, thoracic and mediastinal disorders			With 50 microgram, 4-Hourly: Neonatal asphyxia*[3)]	With 25 microgram, 2-Hourly: Neonatal asphyxia*[3)] Cyanosis neonatal*[4)]
Gastrointestinal disorders	*With 50* microgram*, 4-Hourly:* Nausea[5)] Vomiting[5)]	Diarrhoea *With 25* microgram*, 2-Hourly:* Nausea[5)] Vomiting[5)]		
Skin and				Rash[1)]

subcutaneous tissue disorders				
Pregnancy, puerperium and perinatal conditions	*With 50* microgram, *4-Hourly:* Meconium stain[5)]	Uterine Hyperstimulation[6)] Postpartum haemorrhage *With 25* microgram, *2-Hourly:* Meconium stain[5)]		Premature separation of placenta[7)] Foetal acidosis*[4)] Uterine rupture
General disorders and administration site conditions		Fever Chills[8)]		
Investigations		Apgar score low* Foetal heart rate abnormal*		

* Neonatal adverse reaction.
[1)] Reported with Cytotec. No AEs reported in the selected studies for misoprostol.
[2)] Neonatal seizures were reported in one clinical study at 25 microgram every 2 hours (n = 302 women assessed) and 4 studies with 50 microgram every 4 hours (n = 473 women assessed).
[3)] Neonatal asphyxia was uncommon with 50 microgram every 4 hours. Only two clinical studies at 25 microgram every 2 hours (n = 377 women assessed).
[4)] No AEs reported in the selected studies for misoprostol.
[5)] Nausea, vomiting, meconium stain were common with 25 microgram every 2 hours and very common with 50 microgram every 4 hours.
[6)] Uterine hyperstimulation was reported both with and without foetal heart rate changes.
[7)] Premature separation of placenta was reported in one clinical study at 25 microgram every 2 hours (n = 128 women assessed) and one study with 50 microgram every 4 hours (n = 96 women assessed).
[8)] Chills were reported in two clinical studies at 50 microgram every 4 hours (n = 140 women assessed).

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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

There is no information on overdose with misoprostol.
In case of overdose symptoms (e.g., excessive uterine stimulation causing prolonged or excessive contractions), misoprostol administration should be stopped and supportive care 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 gynecologicals, uterotonics, prostaglandins, ATC code: G02AD06.

Mechanism of action
Misoprostol is a synthetic analogue of Prostaglandin E1 (PGE1). Misoprostol activates cervical ripening and myometrium contraction in all stages of parturition by mimicking the uterotonic action of PGE2 in uterine tissues.

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 microgram 2-hourly
Efficacy and safety data of oral misoprostol for induction of labour are available from meta-analysis of 11 clinical trials where 1,459 women were exposed to oral misoprostol 20 or 25 microgram 2-hourly.

Comparator	Number of studies	Exposure to oral misoprostol 20 or 25 microgram 2-hourly
Intravenous oxytocin	3 (1 DB)	209 (40 in DB)
Vaginal dinoprostone	2 (1 DB)	468 (365 in DB)
Vaginal misoprostol	1	50
Mechanical method	2	454
Oral misoprostol (Titrated)	3	278
TOTAL	**11 (2 DB)**	**1,459 women (405 in DB study)**

DB: Double blind.

The main inclusion criteria in these studies are as follow:

- In two of the three trials comparing against intravenous oxytocin, the main inclusion criterion was term pregnancy (168 women) and in the other study the main inclusion criterion was term pregnancy and Prelabour Rupture of Membranes (PROM) (41 women).
- In all the studies comparing oral misoprostol against vaginal dinoprostone, vaginal misoprostol and titrated oral misoprostol, the main inclusion criterion was term pregnancy (796 women).
- In one study comparing against mechanical method, the main inclusion criterion was term pregnancy (152 women) and in the other study the main inclusion criterion was induction of vaginal birth because of pre-eclampsia or hypertension and around 80% of women were at term pregnancy (302 women).

The double-blind trials Dodd, 2006 and Kashanian, 2020 are considered pivotal and are described in detail in the following:

Dodd, 2006 was a randomised double-blind, active-controlled (vaginal dinoprostone gel) study (N=365/376). Women at term pregnancy (> 36+6 weeks' gestation) 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 foetal heart rate change (FHR) and caesarean sections. There were no statistically significant differences between oral misoprostol and vaginal dinoprostone with regards to vaginal delivery not achieved within 24 hours (oral misoprostol 168/365 (46.0%) versus 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 foetal heart rate changes, caesarean section and caesarean section for foetal distress. There was a statistically significant lower risk of uterine hyperstimulation without foetal heart rate changes in women treated with oral misoprostol.

Kashanian, 2020 was a randomized double-blind, active-controlled (intravenous oxytocin) study (N=40/40). Pregnant women at term pregnancy (gestational age between 40–42 weeks), singleton pregnancy with cephalic presentation, bishop score > 5 and favourable pelvis in the examination were eligible. The primary endpoint was the number of deliveries in the first 24 hours of intervention. The number of deliveries within 24 hours was greater in the misoprostol group (oral misoprostol 40/40 (100%) v intravenous oxytocin 36/40 (90%), P=0.04). The number of deliveries between 6–12 hours, 12–18 hours and 18–24 hours after induction was significantly greater in the misoprostol group. The risk of tachysystole and meconium stain was higher in the misoprostol group compared to the intravenous oxytocin (6/40 (15%) v 1/40 (2.5%), P= 0.04 and 8/40 (20%) v 2/40 (5%), P=0.04, respectively) and duration of start of intervention to proper contractions was longer in the misoprostol group (262.75 ± 113.92 v 69.75 ± 22.67, P<0.01).

Posology 50 microgram 4-hourly
Efficacy and safety data of oral misoprostol for induction of labour are available from meta-analysis of 28 clinical studies where 2,944 women were exposed to oral misoprostol 50 microgram 4-hourly.

Comparator	Number of studies	Exposure to oral misoprostol 50 microgram 4-hourly
Placebo / Expectant	3 (2 DB)	247 (97 in DB)
treatment		
Intravenous oxytocin	3	143

Vaginal dinoprostone	4	322
Vaginal misoprostol	12 (3 DB)	985 (215 in DB)
Mechanical method	5	1215
Oral misoprostol (Titrated)	1 DB	32 in DB study
TOTAL	**28 (6 DB)**	**2,944 women (344 in DB studies)**

DB: Double blind.

The main inclusion criteria in these studies are as follow:

- The main inclusion criterion in all three placebo controlled trials was PROM.
- In one study comparing against intravenous oxytocin, the main inclusion criterion was PROM (52 women). In the second study, the main inclusion criteria were both PROM and term pregnancy (55 women), and in the last study, the main inclusion criterion was term pregnancy (36 women).
- All four studies comparing against dinoprostone were open label studies. In one study, the main inclusion criterion was PROM (31 patients) whereas the main inclusion criterion was preterm (2 studies) or term pregnancy (1 study) for the other three studies (291 women).
- Three of the studies comparing against vaginal misoprostol were double blind studies (215 women). The main inclusion criterion was term pregnancy. One open label study had indication for induction of labour as main inclusion criterion (gestational age: oral misoprostol 38.6 ± 2.2 versus vaginal misoprostol 39.1 ± 2.0, P=0.21; 65 women) and another clinical trial the gestational age was 39.2 ± 1.27 (110 women). The remaining 7 studies (595 women) were open label studies with the main inclusion criterion being term pregnancy, with one on PROM.
- All four studies comparing against mechanical method were open label studies and main inclusion criterion was term pregnancy ("post dated pregnancy" for two of them).
- The one study comparing against oral misoprostol titrated was a double-blind study with term pregnancy as a main inclusion criteria.

The double-blind trials Bennett 1998, 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 misoprostol 50 microgram administered every 4 hours. Pregnant women at term with intact membranes who presented with an indication for induction stratified between low (<7) or high (≥7) Bishop score group were eligible. The primary endpoint was interval from induction to vaginal birth. 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.

Levy 2007 was a double-blind study (N=64/66) investigating the 50 microgram 4-hourly posology against placebo in women with PROM. The primary endpoint was delivery within 24 hours from PROM. The time to delivery was statistically significantly shorter with oral misoprostol compared to placebo (13.7 ± 5.8 vs. 20.3 ± 6.8 h, respectively, P<0.05) with a slight (not statistically significant) increase in the frequency of uterine hyperstimulation. For other safety outcomes, such as oxytocin administration, need of antibiotic treatment and risk of caesarean section, there appeared to be a lower risk in the oral misoprostol group (not statistically significant for caesarian section). No neonates had an Apgar score less than 7 at 5 min.

5.2 Pharmacokinetic properties

Absorption
After oral administration, misoprostol is rapidly absorbed, with peak plasma levels of misoprostol acid occurring after approximately 22 minutes. The mean plasma elimination half-life of misoprostol acid is approximately 40 minutes.

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.

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

Biotransformation and Elimination

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 polar metabolites prior to excretion in the urine mainly.

Renal or hepatic impairment
There are studies showing a trend towards higher Cmax, AUC and t½ 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 non-clinical studies of safety pharmacology, single and repeated dose toxicity, genotoxicity and carcinogenic potential do not reveal a risk hazard at clinically relevant doses.

Reproductive toxicity studies indicated a low potential for effects on male and female fertility and embryotoxicity in animals with relevance for the proposed indication for misoprostol. No clinically relevant effect on pre- and postnatal development in rats was reported.

Fertility and early embryonic development studies in rats showed that misoprostol produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at doses greater than19.3 times the clinical dose in women. Embryo-foetal development studies confirmed the findings of increased resorptions in rabbits at repeated doses greater than 29-fold the maximum daily dose in women.

In mice, misoprostol administered during the first half of the gestation period, was associated with birth defects occurring at clinically relevant doses. A risk of malformations and congenital anomalies associated with foetal death due to exposure to misoprostol during early pregnancy (first trimester), was also noted in humans but this risk is not relevant for proposed indication (see section 4.6). 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
Microcrystalline cellulose
Sodium starch glycolate (Type A)

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 light and moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

oPA/Alu/PVC//Alu blister pack 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

Afyx Therapeutics AS
Slotsmarken 11
2970 Hoersholm
Denmark

8 MARKETING AUTHORISATION NUMBER

PA25312/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2026

10 DATE OF REVISION OF THE TEXT