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misoprostol vaginal insert (Misodel°)

Riskier than *dinoprostone* for inducing labour

● **The vaginal insert containing *misoprostol* has more adverse effects related to uterine hyperactivity than the *dinoprostone* vaginal insert.**

In many countries, including France, labour is artificially triggered in about 15% to 40% of pregnancies, for both medical and non-medical reasons (1,2). One major risk associated with labour induction is the need for emergency Caesarean section due to failure of induction or to fetal heart rate disorders.

When the cervix is "unfavourable", prostaglandins are used first to relax the cervix (**a**). Sometimes they manage to induce or stimulate uterine contractions, otherwise *oxytocin* is used (2).

In France, *dinoprostone*, a prostaglandin E2 analogue, is authorised for labour induction in various forms, including a 10-mg vaginal insert. Tablets of *misoprostol*, a physiological prostaglandin E1 analogue, are sometimes used off-label by various routes, despite ill-defined conditions of use and an uncertain harm-benefit balance (2-4).

A vaginal insert containing 200 microg *misoprostol* (Misodel°, Ferring) has been authorised for labour induction in various European countries. Does it have any advantages over *dinoprostone* vaginal inserts?

No reduction in Caesarean section rates. Clinical evaluation of the vaginal insert containing 200 microg of *misoprostol* is based on a randomised, double-blind, "non-inferiority" trial versus *dinoprostone* 10 mg vaginal inserts in 1358 women, two-thirds of whom had never previously given birth. Labour was induced after at least 37 weeks of gestation in almost every case. All women had an unfavourable cervix and an unscarred uterus (**b**)(4-6).

The rate of Caesarean delivery was about 27% in both groups (4-6). About 1% of women in each group failed to achieve vaginal delivery after the first attempt at induction. The median time between introduction of the insert and vaginal delivery was shorter with *misoprostol* than with *dinoprostone* (22 versus 33 hours, p<0.001). Fewer women in the *misoprostol* group received *oxytocin* prior to delivery (48% versus 74%, p<0.001) (4-6).

Additional risks associated with uterine hyperactivity. In this trial, serious adverse events during childbirth were more frequent with *misoprostol* than with *dinoprostone* (12% versus 7%) (4-6). There were no deaths.

Adverse events associated with excessive uterine activity were significantly more frequent with *misoprostol* than with *dinoprostone* (49% versus 25%). They included uterine tachysystole (13% versus 4%), sometimes requiring treatment (4% versus 1%), or uterine tachysystole associated with fetal heart rate disorders (10% versus 3%) (**c**)(4). The presence of meconium in the amniotic fluid was more frequent in the *misoprostol* group (18% versus 14%), as was the use of tocolytic agents (12% versus 4%) (4).

Certain adverse events of concern for the mother or newborn were also more frequent in the *misoprostol* group, including: uterine rupture (one case versus none); a 5-minute neonatal Apgar score below 7 out of 10 (14 versus 7 cases); fetal acidosis (8 versus 4 cases); and hypoxic-ischaemic neonatal encephalopathy (4 versus 0 cases) (4). In contrast, *dinoprostone* was associated with significantly more infections of the placenta and amniotic fluid (chorioamnionitis) (9% versus 6% with *misoprostol*) and more frequent use of injectable antibiotics during and after childbirth (9% versus 5%), probably due to prolonged labour (4-6).

Similar vaginal inserts, longer misoprostol half-life. The conditions of use and storage of the *dinoprostone* and *misoprostol* vaginal inserts are similar.

According to the respective summaries of product characteristics (SPC), *misoprostol* has a longer half-life than *dinoprostone* (40 minutes versus 1 to 3 minutes) (7,8). This is a disadvantage if, for example, the device has to be removed because of adverse effects (persistent drug exposure of the mother and fetus), or if *oxytocin* needs to be administered (risk of over-stimulating the uterus) (8). According to the SPC, a waiting period of at least 30 minutes must be respected between insert removal and *oxytocin* administration (8).

In practice. As compared with the *dinoprostone* vaginal insert, the *misoprostol* insert reduces time to delivery (about 22 versus 33 hours) as well as the incidence of infections (chorioamnionitis), but it does not avoid the need for Caesarean section. The *misoprostol* insert increases the risk of uterine tachysystole that requires treatment or is associated with fetal heart rate disorders. The *dinoprostone* vaginal insert is safer for both the mother and her newborn.

a- The modified Bishop score evaluates the state of the cervix, based on fetal presentation and four cervical characteristics (dilation, effacement, consistency and position). The score ranges from 0 to 13; the cervix is generally considered unfavourable when the score is 6 or less (ref 2).

b- At inclusion, the average modified Bishop score was about 2.4 in both groups (ref 4).

c- Uterine tachysystole was defined as five or more uterine contractions in 10 minutes over three consecutive 10-minute periods (ref 5).

misoprostol vaginal insert

Misodel°

- **200 microg** of *misoprostol* per vaginal insert (approximately 7 microg/hour released over 24 hours)

prostaglandin E1 analogue

■ **Indication:** *"(...) induction of labour in women with an unfavourable cervix, from 36 weeks of gestation, in whom induction is clinically indicated".*
[European decentralised procedure]

Selected references from Prescrire's literature search.

In response to our request for information, Ferring provided us with administrative documents and published articles.

1- Prescrire Rédaction "Le déclenchement de l'accouchement à terme: la qualité pour tous vue par des usagers" *Rev Prescrire* 2010 ; **30** (322): 625-626.
2- Wing DA et al. "Induction of labor", "Techniques for ripening the unfavorable cervix prior to induction" UpToDate. www.uptodate.com accessed 13 June 2015: 41 pages.
3- Prescrire Editorial Staff "Misoprostol: serious cardiovascular events, even after a single dose" *Prescrire Int* 2015; **24** (162): 183-184.
4- HAS - Commission de la transparence "Avis-Misodel" 7 January 2015: 20 pages.
5- Wing DA et al. "Misoprostol vaginal insert and time to vaginal delivery: a randomized controlled trial" *Obstet Gynecol* 2013 ; **122** (2): 201-209.
6- Therapeutic Goods Administration "Australian Public Assessment Report for misoprostol" April 2014: 49 pages.
7- ANSM "RCP-Propress" 12 March 2015: 5 pages.
8- ANSM "RCP-Misodel" 6 March 2014: 8 pages.