BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

MISODEL (misoprostol), uterotonic prostaglandin

Clinical benefit insufficient in Induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.

Main points

- MISODEL has Marketing Authorisation for Induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.
- In a double-blind study of MISODEL versus PROPESS (vaginal delivery system releasing 10 mg of dinoprostone, prostaglandin E2), the interval between the initiation of treatment and delivery (primary endpoint) was shorter in the MISODEL group (median: 21.5 hours) than in the PROPESS group (median: 32.6 hours, p < 0.001). This study demonstrated that MISODEL is not inferior to PROPESS in respect of the percentage of caesareans. Foetal and neonatal safety criteria should have been chosen as the primary efficacy endpoint.
- Taking into account the excessive effect of misoprostol on uterine activity at the dose contained in MISODEL (200 µg), without any advantage in terms of maternal and/or foetal morbidity in comparison with intravaginal administration of prostaglandin E2, MISODEL has no place in the therapeutic strategy.

Therapeutic use

The guidelines concerning the artificial induction of labour when the cervix is unfavourable are, depending on the medical indications:

- post-term pregnancy: in the absence of delivery by , 41 weeks 6 days of gestation, induction of labour is recommended, and can be preceded by cervical ripening with prostaglandins,
- diabetes: the management of insulin-dependent diabetes need a multidisciplinary decision on a case-by-case basis. If the diabetes is poorly controlled or has an impact on the foetus, it is recommended that 38 weeks 6 days of gestation should not be exceeded. In the case of controlled gestational diabetes and with no impact on the foetus, there is no justification for following a procedure differing from that in a normal pregnancy,
- twin pregnancy: even though the data in the literature do not permit any conclusions to be drawn about the benefits of systematic induction in the case of an uncomplicated twin pregnancy, it is recommended that 39 weeks 6 days of gestation should not be exceeded,
- intrauterine growth restriction: there are insufficient data to permit an assessment of the advantages and risks of the artificial induction of labour in the event of intrauterine growth restriction at term. The cessation of growth is a high-risk perinatal situation that can require delivery (induction of labour or caesarean) after consultation with the in-house paediatrician,
- pre-eclampsia should require delivery of the infant (induction of labour or caesarean).

Artificial induction of labour is appropriate for pregnant women at or close to term who have not commenced labour, whatever the condition of the membranes. The use of prostaglandin E2 (PGE2) is preferable to the use of oxytocin for the induction of labour in unfavourable cervix. The use of PGE2 involves a risk of hyperkinesis and/or hypertonus, which could be accompanied by foetal heart rate abnormalities.

Misoprostol, at any dose level, is contraindicated in the presence of uterine scarring. Intravaginal forms of prostaglandin E2 are to be preferred to intracervical form for induction of labor, face to equal efficacy, this route of administration has been found to be less aggressive.

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Place of the medicinal product in the therapeutic strategy

Because of the excessive effect of misoprostol on uterine activity at the dose in MISODEL (200 µg), which could explain the observed adverse effects, and in the absence of any advantage in terms of maternal and/or foetal morbidity compared with intravaginal administration of prostaglandin E2, this proprietary medicinal product does not have any role in the induction of labour in women presenting an unfavourable cervix from 36 weeks of gestation and with a viable foetus.

Clinical data

In a double-blind study that compared MISODEL (misoprostol) to PROPESS (vaginal delivery system releasing 10 mg of dinoprostone, prostaglandin E2), the time to delivery during the first hospitalisation (primary endpoint) was shorter in the MISODEL group (median: 21.5 hours) than in the PROPESS group (median: 32.6 hours, \( p < 0.001 \)). The choice of “time to delivery” as the primary efficacy endpoint is debatable, and led to the 200 µg dose being preferred to the 100 µg dose, despite the better safety of the 100 µg dose that was observed in the phase II studies. In fact, even though the time to delivery is important for the comfort of the woman in labour and for the physicians providing care, the foetal and neonatal safety criteria should have been chosen as the primary efficacy endpoint.

The percentage of caesareans during the first hospitalisation was 25.96% in the MISODEL group and 27.06% in the PROPESS group, or a difference between the groups of -1.10%. This study did not demonstrate the non-inferiority of MISODEL compared to PROPESS for this criterion.

In a dose-finding study, 58% of the 131 patients treated with the vaginal delivery system containing 200 µg of misoprostol (MISODEL) gave birth vaginally within 24 hours, and 22.9% gave birth by caesarean. In another dose-finding study, 90% of the 30 patients treated with the vaginal delivery system containing 200 µg of misoprostol (MISODEL) gave birth vaginally and 10% delivered by caesarean. The mean time between the initiation of treatment and delivery by the vaginal route was 10.6 hours.

In the study of MISODEL versus PROPESS, serious and non-serious adverse events during delivery and in association with uterine hyperactivity were more common in the MISODEL group: any uterine hyperkinesis; 49.1% in the MISODEL group versus 24.6% in the PROPESS group; this includes uterine hyperkinesis with foetal heart rate abnormalities (10.3% versus 2.6%) and the use of tocolysis (12.2 versus 4.1%). There was no difference between the frequencies of foetal heart rate abnormalities in the MISODEL and PROPESS groups (24.9% versus 25.7%).

The adverse events most often reported in the PROPESS group were arrest of labour and chorioamnionitis. The use of intravenous/intramuscular antibiotics during labour and post-partum was more common in this treatment group.

Serious adverse events, though rare, have been reported during the use in voluntary termination of pregnancy VTOP, of proprietary medicinal products containing misoprostol (GYMISO and CYTOTEC) off label in case of Cytotec: myocardial infarction, cerebrovascular accidents.

Special prescribing conditions

Medicinal product reserved for hospital use.

Benefit of the medicinal product

The actual benefit of MISODEL is insufficient to justify reimbursement by National Insurance.

The Transparency Committee does not recommend inclusion on the list of reimbursable products for hospital use.

This document was created on the basis of the Transparency Committee Opinion of 07 January 2015 (CT-13662) and is available at www.has-sante.fr

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement by the National Health Insurance.