HAUTE AUTORITÉ DE SANTÉ

GYNAECOLOGY-OBSTETRICS
New medicinal product
April 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

ANGUSTA 25 µg (misoprostol), oral route, uterotonic

Low clinical benefit in induction of labour in the absence of cervical ripening, only in the event of medically-justified induced labour, but no clinical benefit demonstrated in the therapeutic strategy

Insufficient clinical benefit in induction of labour with cervical ripening or in the event of non-medically-justified induced labour.

Main points

- ANGUSTA 25 µg, oral route, has MA in labour induction. The dosage is 25 µg every 2 h or 50 µg every 4 h. The maximum dose is 200 micrograms every 24 h.
- No studies on misoprostol have studied ANGUSTA 25 µg specifically. They were carried out on the proprietary medicinal product CYTOTEC at different doses (in the form of fractions of tablet oral solution made up from CYTOTEC). The bioequivalence between the two medicinal products has not been demonstrated.
- Data from literature suggest misoprostol administered by oral route to be effective on the reduction in the number of caesareans or on the reduction in the number of births by vaginal route not resulting in expulsion within 24 hours.
- However, the misoprostol administration regimens (some of which are off-label) used in the data from the relevant literature, among which none correspond to the dosages in the ANGUSTA MA cannot be used to position this medicinal product with respect to its comparators, in terms of efficacy and safety.

Therapeutic strategy

- Ocytocin is currently the gold standard method for induction of labour on cervical ripening at 41 weeks' amenorrhoea (WA) and later.
  If it is necessary to induce labour on a non-ripe cervix, prostaglandin E2 (PGE2) should be preferred to ocytocin. It provides the possibility of less frequent use of ocytocin and of reduction of the doses. PGE2 use can cause uterine hyperkinesia and/or hypertonia, and foetal arrhythmia.
- CYTOTEC (misoprostol, PGE1) has been used off-label in obstetrics to induce labour from 37 weeks' amenorrhoea, especially by vaginal route, without any data on safety of use predicting a favourable benefit/risk balance in this indication (induction of labour), regardless of the route of administration. It is no longer marketed.
- **Role of the medicinal product in the therapeutic strategy**
  The data available cannot be used to position ANGUSTA amongst its comparators in terms of safety.
  ANGUSTA is useful for induction of labour on a non-ripe cervix by oral route, in medically-justified situations, where the other induction methods cited are not available.

Clinical data

- No studies on misoprostol have studied ANGUSTA 25 µg specifically. They were carried out with CYTOTEC (in the form of fractions of tablet oral solution made up from CYTOTEC). Bioequivalence between ANGUSTA 25 µg and CYTOTEC was not demonstrated,
- A systematic Cochrane review with meta-analyses suggested misoprostol administered by oral route to be effective compared to a placebo or to one of the relevant comparators (prostaglandin E2 administered by vaginal route) mainly in terms of the reduction in the number of caesareans. In light of the many tests conducted, inclusion of two off-label doses (100 and 200 µg) in the comparisons, the inclusion of studies having used lower doses in the analyses on the 25 µg dose, the fact that these studies were not carried out with ANGUSTA but with powdered CYTOTEC solutions or capsules, the results cannot be considered to be robust as to the efficacy of ANGUSTA 25 µg.
  Among the comparisons from the Cochrane review, the percentage admission of newborns to the intensive care unit was significantly lower among women having received misoprostol compared to those not having received treatment or having received a placebo.
- A systematic review with network meta-analysis concluded on placebo-controlled efficacy for the 3 misoprostol oral administration regimens and the relevant comparators in terms of reduction in births by vaginal route not resulting in expulsion within 24 hours. The misoprostol regimens used in this meta-analysis cannot be used to position the ANGUSTA 25 µg doses in the MA with respect to the comparators in terms of efficacy.
- A study exhibiting methodological bias (open-label study, ITT analysis, no adjustment of the alpha risk) concluded on the non-inferiority of 50 µg of oral misoprostol compared to insertion of a Foley catheter in induction of labour at term on non-ripe cervix on a composite endpoint: neonatal anoxia (cord arterial pH ≤7.05 or Apgar score after 5 min <7) or post-partum haemorrhage.

Special prescription requirements

- Medicinal product for hospital use only

Benefit of the medicinal product

- The actual clinical benefit* of ANGUSTA is
  - low in induction of labour with an unripe cervix, only in the event of medically-justified induced labour.
  - insufficient in induction of labour with cervical ripening or in the event of non-medically-justified induced labour.
- ANGUSTA does not provide an improvement in actual clinical benefit (IACB V) in the current therapeutic strategy to induce labour with non-ripening of the cervix, in medically-justified situations involving the relevant comparators.
- Approved for reimbursement for hospital treatment.

HAS
HAUTE AUTORITÉ DE SANTÉ

This document was drafted on the basis of the Transparency Committee opinion dated 18 April 2018 (CT-16829) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"