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National Health Care Institute
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Our reference
2022038626

Date 8 March 2023
Re: GVS advice mifepristone (Mifegyne®)

Dear Mr Kuipers,

In a letter of 12 September 2022 (reference 401645-1032952 GMT), you asked the National Health Care Institute to assess the primary care application of mifepristone tablet 200 mg (Mifegyne®) for miscarriages, and to examine whether mifepristone can be included in the Medicine Reimbursement System (GVS) for the treatment of miscarriages, as described in the revised Guideline for Miscarriages of the Dutch Society for Obstetrics and Gynaecology (NVOG). The Minister's request therefore does not apply to the application of mifepristone for the discontinuation of an intact pregnancy at home.

The National Health Care Institute has now completed the assessment.

Background

In 2020, the NVOG revised the Guideline for Miscarriages. This review includes a recommendation, based on available scientific evidence, to provide a combination therapy of mifepristone and misoprostol, rather than just misoprostol, in case of medical management for miscarriage (non-vital pregnancy).

Recently, the Ministry of Health, Welfare and Sport (VWS) and the National Health Care Institute have received various alerts from the professional group about the lack of reimbursement of mifepristone in the primary healthcare treatment of miscarriage. Mifepristone is not included in the GVS, while the other medicinal product, misoprostol (Cytotec®, tablet 200 mcg), is included in the GVS.

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Assessment

The revised NVOG Guideline on Miscarriages focuses on the treatment of patients with symptoms that may indicate a miscarriage or non-vital pregnancy, such as abdominal pain and/or blood loss up to 16 weeks of amenorrhea. In a non-vital (=non-intact) pregnancy, it is clear that the foetus is not viable (e.g., there is no heart action any more), but there are as yet no signs of a miscarriage in progress.

Although surgical treatment (curettage, suction or otherwise) is the most effective treatment in case of a miscarriage, observational research has shown that this creates an increased risk of uterine adhesions and an increased risk of premature birth in a subsequent pregnancy. For these reasons, less intrusive options such as a wait-and-see policy and, if desired, medicinal management should always be considered first.

If medical management is chosen for a miscarriage or non-vital pregnancy, the combination of mifepristone plus misoprostol is now preferable to a treatment with misoprostol alone.

Substantive assessment

Therapeutic value

Mifepristone tablet 200 mg is a steroid with antiprogestagenic action due to competitive blockade of progesterone receptors. This inhibits the effects of progesterone that contribute to maintaining the pregnancy. It also makes the uterine wall sensitive to the effects of prostaglandins during pregnancy, which induces labour. During the first trimester, pre-treatment with mifepristone causes a widening and opening of the cervix. It also has some antiglucocorticoid activity. Mifepristone is registered for

- The medicinal termination of a developing intrauterine pregnancy, in combination with a prostaglandin analogue, to up to 63 days of amenorrhea.
- Softening and dilatation of the cervix prior to a surgical abortion during the first trimester.
- Preparation of the effect of prostaglandin analogues during the termination of the pregnancy after the first trimester for medical reasons.
- Induction of contractions in case of an intrauterine foetal death, if the use of prostaglandin or oxytocin is not possible.

Misoprostol tablet 200 mcg is a synthetic analogue of prostaglandin E1; it is registered for the prevention of NSAID-induced stomach and intestinal ulcers, and thus acts as an antacid. Misoprostol has as an important side effect the maturation of the cervix and uterine contractions. This medicinal product is therefore used (off-label) for the medical management of a miscarriage.

On the basis of three clinical studies, we can conclude that treatment with 200 mg of mifepristone oral 24-48 hours prior to treatment with misoprostol (800 mcg (=4 tablets at a time) as high as possible in the vagina) probably results in a higher percentage of successful treatments than treatments with only misoprostol in patients with a miscarriage or non-vital pregnancy up to 16 weeks of amenorrhea (see Annex).

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Conclusions of interchangeability

Based on the criteria for interchangeability, it can be concluded that mifepristone is not interchangeable with any other medicinal product in the GVS. There is no medicinal product with a corresponding indication area in the GVS which allows the interchangeability to be investigated for the indication of a miscarriage and non-vital pregnancy indication up to 16 weeks of amenorrhea, in combination with misoprostol. Mifepristone is thus eligible for inclusion in list 1B.

Budget impact analysis

One 200 mg mifepristone tablet costs €26.05. Based on 20,000 women who have a miscarriage, the maximum additional costs from adding mifepristone to the treatment with misoprostol will amount to €521,000. However, this is an overestimation because not all women with a miscarriage will receive medical management.

The higher success rate by adding mifepristone could, in essence, result in cost savings due to fewer surgical procedures and/or hospitalisation.

Advice

On the basis of the above considerations, mifepristone is eligible for inclusion in List 1B. Based on our assessment, which is only related to the application in case of miscarriage or non-vital pregnancy, we advise you to set conditions for reimbursement:

Condition
(off-label) In combination with misoprostol for the medical management of a miscarriage or non-vital pregnancy up to and including 16 weeks of amenorrhea.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board