Mifepristone - misoprostol

Statut de médicament essentiel ✓

Section: 22. Medicines for reproductive health and perinatal care > 22.3. Uterotonics

Codes ATC: G03XB51

Indication	Unspecified time of fetal death, cause not specified Code ICD11: KD3B.Z
INN	Mifepristone + misoprostol
Type de médicament	Chemical agent
Type de liste	Liste de base
Additional notes	Where permitted under national law and where culturally acceptable.
Formulations	Oral > Solid: 200 mg + 200 µg ; 200 mg [1] + 200 µg [4] in co-package
Historique des statuts LME	Ajouté pour la première fois en 2023 (TRS 1049)
Sexe	Féminin
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Mifepristone - misoprostol
DrugBank	Mifepristone, Misoprostol

Recommandation du comité d'experts

The Expert Committee noted the evidence from a randomized controlled trial and systematic review that assessed medical management of IUFD that showed the combination regimen of mifepristone and misoprostol was associated with a higher proportion of complete fetal expulsion at 24 hours as well as with lower time to complete expulsion compared with misoprostol alone, without increased severe adverse events or requirement for surgery. While the Committee noted that the available evidence was graded low certainty, indirect evidence on the use of mifepristone and misoprostol in the management of medical abortion showed high effectiveness. The Committee also noted side-effects associated with the regimen were minor and that uterine rupture was very rare. Additionally, the Committee noted that medical management of IUFD with mifepristone and misoprostol has been recommended in the WHO guidelines on abortion care since 2018. The Committee also noted that mifepristone and misoprostol were widely available and were prequalified by WHO. The Committee emphasized the importance of providing patients and health care providers with multiple choices for the management of IUFD. The Expert Committee therefore recommended that the listing for mifepristone – misoprostol on the core list of the EML be extended to include the new indication of medical management of IUFD.

Contexte

Mifepristone and misoprostol have not been previously considered for inclusion on the EML for medical management of IUFD. No other medicines are currently included on the EML for use in medical management of this indication. The combination of mifepristone and misoprostol has been included on the EML since 2005 for medical abortion. Misoprostol 200 microgram tablets are also listed individually for the management of incomplete abortion and miscarriage, and prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used.

Pertinence pour la santé publique

About 1% of all pregnancies are complicated by IUFD (1). IUFD refers to the clinical condition where the fetus is no longer alive, but the uterus has not yet started to expel its contents and the cervix remains closed. Some of the clinical findings suggestive of IUFD include vaginal bleeding, absent fetal heartbeat on electronic auscultation, a failure to feel fetal movements or a uterus that is significantly smaller than the expected size (2). Although the exact incidence of IUFD is not known, about 50% occur between 20 and 27 weeks of gestation (mainly from 20 to 23 weeks) (3). Management options include expectant, surgical abortion with dilation and evacuation, or medical management. Several studies have demonstrated that IUFD can be associated with haemorrhage and sepsis leading to increased morbidity and mortality. After an IUFD, the need for a blood transfusion and blood products ranges from 18% to 28% (4,5). IUFD can also lead to a rare but unique complication of disseminated intravascular coagulation (6,7). The presence of disseminated intravascular coagulation was a substantial risk for haemorrhage (8,9). Evidence of disseminated intravascular coagulation was observed in 10% of IUFD cases within 4 weeks of fetal demise. Timely management of IUFD has been shown to decrease the risk of severe coagulation abnormalities (7,10).

Bénéfices

Studies that assessed medical management of IUFD consistently showed that the combination regimen of mifepristone and misoprostol had a high success rate of fetal expulsion with a short induction to abortion interval (11–13). A randomized controlled trial that compared combination regimen of mifepristone and misoprostol with misoprostol alone for IUFD showed that the combination regimen was significantly more successful in achieving fetal expulsion within 24 hours (92.5% versus 71.2%; relative risk (RR) 1.3, 95% confidence interval (CI) 1.1 to 1.6) (11). In addition, the study demonstrated a significantly shorter mean fetal expulsion time with the combination regimen (9.8 versus 16.3 hours; mean difference (MD) 6.5 hours, 95% CI 4.5 to 8.5 hours). This finding has clinical and health system implications in terms of shorter facility stay, bed occupancy and patient turnover rate. Another study compared two dose regimens of misoprostol (200 micrograms and 400 micrograms) for second-trimester termination of viable and non-viable pregnancies (12). This study showed that in the combination regimen of mifepristone and misoprostol, 400 microgram misoprostol dosing achieved a shorter expulsion time compared with a 200 microgram dosing (9.3 versus 11.6 hours). A cohort study assessed the effect of pretreatment with mifepristone 24–48 hours before misoprostol compared with misoprostol alone. Women with IUFD who received mifepristone had a shorter fetal expulsion time than those treated with misoprostol alone (10.6 hours versus 16.2 hours; P = 0.04). In addition, mifepristone pretreatment significantly reduced the risk of infection (P = 0.049) and lowered the need for pain relief (P = 0.022) (13). A recent systematic review assessed the effectiveness, safety and acceptability of medical management of IUFD at ≥ 14 to ≤ 28 weeks of gestation (14). The review included 16 randomized controlled trials that compared: regimens of mifepristone used in combination with misoprostol versus misoprostol alone; different doses of misoprostol after administration of mifepristone; different doses of misoprostol with or without a loading dose; different routes of administration of misoprostol; and different preparations of misoprostol. The trials included were conducted in 17 countries providing information on the varying country contexts in which such services may be provided. Of these 17 countries, six were lower middle-income economies, seven were upper middle-income economies and four were high-income economies. Treatment with combination regimen of mifepristone and misoprostol had higher rates of complete abortion within 24 hours (RR 1.18, 95% CI, 0.91 to 1.53; very low-certainty evidence) and a shorter expulsion time (6.3 hours shorter (95% CI −9.3 to −3.4 hours; very low-certainty evidence) than misoprostol alone. Serious adverse events such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete removal of products, or death were not reported. Treatment with 400 micrograms misoprostol in the combination regimen showed higher rates of complete abortion within 24 hours (RR 0.90, 95% CI 0.74 to 1.10; low-certainty evidence) and lower rates of serious adverse events (RR 1.40, 95% CI 0.32 to 6.05; very low-certainty evidence) than 200 microgram misoprostol dosing. Overall, women were satisfied with their treatment and found the pain associated with the induction less than or the same as they expected. Over the past 2 decades, a number of clinical studies have been conducted to assess the clinical effectiveness and safety of medical abortion in different settings (15–19). Systematic reviews of these studies have led to refined regimens of medical abortion using a combination of mifepristone and misoprostol (20–22). The WHO guidelines have included recommendations for the use of this combination regimen for medical abortion since 2012 (23). The clinical effectiveness of this regimen was as high as 95%. Serious adverse events such as transfusion or hospitalization were reported rarely (21,22,24). Such findings were consistently reported in several individual clinical trials and systematic reviews. Although these studies focused on induced abortion, given the same mechanism of action, a similar outcome can be reasonably inferred on the use of the combination regimen in similar clinical contexts. As such,

these findings can serve as indirect evidence to demonstrate the applicability of the combination regimen for medical management of IUFD.

Torts

Although it is difficult to estimate the total number of medical abortions using mifepristone and misoprostol that have taken place globally, research published in 2017 reported that more than 3 million people in the United States have had a medical abortion using a regimen containing mifepristone since approval by the Food and Drug Administration in 2000 (25). More recently, a study by the Guttmacher Institute estimated that 12.7 million medical abortions occur annually in India (26). Abdominal pain and cramping are expected side-effects of medical abortion, but their incidence is not systematically reported in clinical studies. Treatment with mifepristone and misoprostol is intended to induce uterine bleeding and cramping and as such, bleeding and cramping are expected consequences of the abortion process (27). These side-effects are minor and can be managed with widely available analgesic medications such as non-steroidal anti-inflammatory drugs (24). WHO's 2022 abortion care guideline states that women requesting abortion should always be offered medication for pain management. Pain medications can be offered by various cadres of health care providers (28). All women seeking abortion should be counselled about common side-effects after mifepristone and misoprostol medical abortion and told how they can be managed. In deciding on a course of treatment, some pregnant women may choose regimens with routes of misoprostol that may be associated with more side-effects but may be more consistent with their wishes and expectations of acceptability and overall satisfaction. The most commonly reported adverse reactions (> 15%) for mifepristone and misoprostol include nausea, weakness, fever/chills, vomiting, headache, diarrhoea and dizziness. The frequency of adverse reactions varies between studies and depends on many factors, including the patient population and gestational age (11,12). Uterine rupture is a rare complication and is usually associated with a prior uterine scar and/or very high doses of misoprostol. A systematic review of second-trimester abortion with misoprostol showed the risk of uterine rupture was 0.28% in women with prior caesarean birth, whereas the risk was 0.04% in those without prior caesarean delivery (29). WHO guidelines highlight the need for sound clinical judgement and health system preparedness for emergency management of uterine rupture in these very rare events (28). Analysis of clinical studies involving 30 966 participants who used a combination regimen for medical abortion up to 70 days gestation showed serious adverse events to be very low (reported in < 0.5% of women). No differences were seen in the rate or type of serious adverse reaction by geographical location. A summary of the reported serious adverse reaction is shown in Table 28 (refer TRS 1049) (30). Safety data published in the United States 16 years after mifepristone's approval found an estimated mifepristone-associated mortality rate of 0.00063% (25,30). Studies involving mifepristone and misoprostol among more than 423 000 women globally reported very low rates (0.01% to 0.7%) of non-fatal serious adverse events such as hospital admission, blood transfusion or serious infection after the use of mifepristone. These events were almost always treatable without permanent sequelae (25).

Rapport coût/efficacité

The price of mifepristone and misoprostol, individually and copackaged, varies widely by geographical location. The legal status of abortion, willing marketers and distributors, and a perceived sustainable market all affect the cost to the buyer. Market flexibility is being regulated by the increasing number of new products entering markets. The United Nations Population Fund (UNFPA) product catalogue contains different commodities related to sexual and reproductive health. All products included in this catalogue are WHO prequalified or authorized for use by a stringent regulatory authority. The UNFPA product catalogue currently lists mifepristone 200 mg at a price of US$ 16 per tablet and misoprostol 200 micrograms at US$ 13.92 for a pack of 40 tablets (35). A large study on the price of medical abortion commodities in different settings showed unit prices of mifepristone, misoprostol and combi-packs varied greatly (36). The median price of mifepristone per tablet was US$ 11.78 (range US$ 1.77 to 37.83). The price was highest in Latin America and the Caribbean (US$ 24.47) and lowest in South and South-east Asia (US$ 5.20). In Africa, mifepristone prices ranged from US$ 6.00 to 21.86. The most commonly identified mifepristone brand had a median price to the consumer of US$ 10.35 per tablet (range US$ 3.02 to 17.91). The median price per misoprostol tablet was US$ 0.63 (range US$ 0.09 to 27.63). The price of misoprostol also showed great variation within and between countries and regions, with a similar pattern for mifepristone (highest in Latin America and the Caribbean and lowest in South and South-east Asia). The median price of copackaged mifepristone and misoprostol was US$ 11.14 (range US$ 3.50 to 35.86) per pack (36). The price range for the most frequently identified brand was also wide (US$ 4.02 to 20.05); this product had a median price per pack of US$ 15.44.

Directives de l'OMS

Medical management of IUFD with mifepristone and misoprostol has been a recommendation in the WHO guidelines since 2018 (31) and was recently updated in 2022 (28). This updated guideline recommends medical management of IUFD at gestational ages ≥ 14 to ≤ 28 weeks using a combination of 200 mg of mifepristone administered orally followed 1–2 days later by repeat doses of 400 micrograms misoprostol administered sublingually or vaginally every 4–6 hours. Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. This regimen was shown to have a higher rate of complete abortion within 24 hours and a shorter induction time (14). The certainty of the evidence was low to very low, downgraded due to imprecision arising from a small sample size. Difficulties in reaching large sample sizes have been a limitation of abortion-related studies and these studies may fall short of statistically significant findings. In such circumstances, it is important to consider outcomes in their totality taking into account other important parameters such as the value and preference of end-users and implications to the health system (28). The WHO guideline on abortion care recognizes medical management of IUFD with combination regimen can be performed by a wide range of health care providers including midlevel (non-physician) health care providers (28). Studies have been done on medical abortion for pregnancies at gestational ages ≥ 12 weeks as a facility-based procedure. Based on extrapolation from these studies, the WHO recommends women undergoing medical management of IUFD with the combination regimen should remain under observation until the process is complete (28). Recommendations in other current clinical guidelines The clinical recommendation from the United States Society of Family Planning for interruption of nonviable pregnancy between 24 and 28 weeks includes the administration of a mifepristone and misoprostol regimen. This regimen is noted to have a shortened expulsion time (32). The American College of Obstetricians and Gynecologists also recommends the use of mifepristone plus misoprostol for IUFD. Either 200 mg or 600 mg of oral mifepristone 24–48 hours before misoprostol reduces the time to delivery compared with misoprostol alone (33). These are grade B recommendations as per the United States Preventive Services Task Force (there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial). Similarly, the Royal College of Obstetricians and Gynaecologists recommends a combination of a single dose of 200 mg of mifepristone with misoprostol for the management of IUFD. This is a grade B recommendation, which was developed from high-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal (34).

Disponibilité

Mifepristone and misoprostol, both individually and copackaged, are widely and increasingly available globally (36,37). Branded and generic products are available. Misoprostol and copackaged mifepristone + misoprostol are included on the WHO List of Prequalified Finished Pharmaceutical Products.

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