Mifepristone - misoprostol

Statut de médicament essentiel ✓

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

Codes ATC: G03XB51

Indication	Induced abortion Code ICD11: JA00.1
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 2005 (TRS 933) Modifié en 2019 (TRS 1021)
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 recommended moving mifepristone-misoprostol from the complememtary to the core list of the EML, and removal of the note that states that close medical supervision is required, on the basis of the strong evidence presented that close medical supervision is not required for its safe and effective use. The Committee also recommended the addition of a co-packaged presentation of mifepristone and misoprostol to the core list of the EML. Recalling that their role and responsibility is to provide WHO with technical guidance in relation to the selection and use of essential medicines, the Expert Committee noted that its mandate does not extend to providing advice on the statement “Where permitted under national law and where culturally acceptable”.

Contexte

Mifepristone-misoprostol has been included on the EML for use in medical abortion since 2005. The Committee recommended listing on the complementary list with the note regarding the requirement for close medical supervision. In reviewing the recommendation by the Committee, the Director-General sought clarification from the Committee regarding the risks and benefits of mifepristone-misoprostol. The Director-General subsequently made the decision to approve listing mifepristone-misoprostol on the EML with an additional note: “Where permitted under national law and where culturally acceptable.” The current application requested the following changes to the current listing on the EML of mifepristone-misoprostol: • transfer from the complementary to the core list; • removal of the note stating “Requires close medical supervision”; • removal of the boxed text stating “Where permitted under national law and where culturally acceptable”; • addition of a co-packaged presentation of mifepristone and misoprostol.

Pertinence pour la santé publique

Despite the major advances in management of abortion over the past two decades, of the 55.7 million abortions that occurred worldwide each year between 2010–2014, 30.6 million (54.9%) were considered safe, 17.1 million (30.7%) are classified as less safe and 8.0 million (14.4%) were considered least safe according to new safety classifications. 24.3 million (97%) of unsafe abortions occur in low- and middle-income countries (LMICs) (1). In LMICs, around 7 million women are admitted to hospitals annually as a result of unsafe abortion (2). Globally, between 4.7% and 13% of maternal deaths have been attributed to unsafe abortion (3).

Bénéfices

Evidence for the clinical effectiveness of mifepristone-misoprostol was evaluated at the time of original listing in 2005 (4). Updated evidence was considered as part of the development process for the 2018 WHO guidelines for medical management of abortion and continues to support the effectiveness, safety and acceptability of mifepristone-misoprostol (5). Support for less medicalized service delivery of mifepristone-misoprostol exists in a number of WHO guidelines, clinical guidance and systematic reviews (5–11). Specifically, the WHO 2015 Health worker roles in providing safe abortion care and post-abortion contraception (7) and the 2018 Medical management of abortion guidance (5), state that administration of mifepristone-misoprostol does not require direct medical supervision or specialized care. WHO recommends that pregnant persons should be provided information and access to health care providers if they are experiencing signs of ongoing pregnancy or for any other medical reasons (5, 7, 8, 12). One health worker can provide the entire package, but it is equally possible for sub-tasks to be performed by different health workers and at different locations. The application states that specialized diagnostics or treatment are not needed (6). Provision of care generally requires access to quality mifepristone and misoprostol in the correct dosages, instructions on how to use them (including dating of gestational age) and information about how to recognize complications (e.g. in the event of very heavy and/or prolonged bleeding) and where to seek help. Ultrasound scanning is not routinely required (5–8), and routine use of antibiotics and testing for sexually transmitted infections is not recommended. In the event of undiagnosed ectopic pregnancy, heavy, ongoing bleeding and/or retained products of conception that may not evacuate on its own, the pregnant person may require referral to a higher level care (6–8). Evidence supports safe and effective provision of medical abortion for pregnancies less than 12 weeks uterine size by the following health care cadres: auxiliary nurses, auxiliary nurse midwives, nurses, midwives, associate and advanced associate clinicians, non-specialist and specialist doctors (5–9, 13–17). It is recommended that every primary care health service delivery point have staff (regardless of their cadre) trained and competent to take a medical history, perform a bimanual and abdominal examination and establish a referral network with higher level facilities and/or providers who are available to manage complications in the rare event that they may arise. The application stated that desired benefit of co-packaged mifepristone-misoprostol is to ensure availability of quality-assured products with consistent and clear dosing. A recent study of the provision of medical abortion and post-abortion contraception by mid-level health care providers in Kyrgyzstan involved training midwives and family nurses to provide medical abortion with co-packaged mifepristone-misoprostol (18). Results demonstrated that trained midwives and nurses can provide medical abortion safely and effectively. Although the study did not compare co-packaged mifepristone-misoprostol with individually packaged drugs, the authors recommended registration and market availability of high quality co-packaged mifepristone-misoprostol as a strategy to facilitate the scale up of safe abortion in Kyrgyzstan.

Torts

Evidence for the safety of mifepristone-misoprostol was evaluated at the time of original listing in 2005 (4). Recently published safety data from the United States reported an estimated mifepristone-associated mortality rate of 0.00063% (19). Studies including mifepristone-misoprostol medical abortions among more than 423 000 persons 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 use of mifepristone (19). In addition, a pooled analysis of serious adverse reactions including data from 30 966 clinical study participants presenting for mifepristone-misoprostol medical abortion through 70 days gestation found no differences in rate or type of serious adverse reaction by geographical location (20). Serious adverse reaction rates were reported in <0.5% of study participants and include atypical presentation of infection, sepsis and prolonged heavy bleeding/hemorrhage (20). These events were typically treatable without permanent sequelae. The 2015 WHO recommendations on health worker roles in providing safe abortion care

and post-abortion contraception highlight that the most commonly experienced non-life threatening side-effects can be managed in primary care and outpatient settings by various cadres of health care providers (7). Evidence suggests that the provision of medical abortion by mid-level providers has no impact on the safety or efficacy of the abortion process (21). Self-management of medical abortion with mifepristone-misoprostol without the direct supervision of a health care provider is recommended in specific circumstances, in which pregnant persons have the appropriate information and access to health services should they be wanted or required (5–7, 22).

Preuves supplémentaires

N/A

Rapport coût/efficacité

The price of individual and co-packaged mifepristone and misoprostol varies globally. The legal status of abortion, willing marketers and distributors and a perceived sustainable market all impact the cost to the buyer. Market flexibility is being regulated by the increasing number of new products in markets – both individual and co-packaged products. It is hoped that increasing access to quality co-packaged medicines for medical abortion will drive prices down. The application stated that when purchased individually, the average cost of mifepristone and misoprostol for one medical abortion ranges from US$ 4.19 to US$ 10.03, while costs for the co-packaged product range from US$ 3.75 to US$ 11.75.

Directives de l'OMS

WHO Safe abortion: Technical and policy guidance (6) was first issued in 2003 and updated in 2012. It includes recommendations for clinical care, while also addressing policy, programmatic and health systems considerations in the provision of safe abortion. WHO Clinical practice handbook for safe abortion (8) was issued in 2014. It provides guidance to providers with requisite skills and training necessary to provide safe abortion and/or treat complications of unsafe abortion. WHO Health worker roles in providing safe abortion and post-abortion contraception (7) was issued in 2015 and contains recommendations on the roles of various health workers in the provision of abortion care, as well as self-management of medical abortion. WHO Medical management of abortion (5) guidelines issued in 2018 includes the following recommendations on medical abortion regimens for management of induced abortion: For the medical management of induced abortion at less than 12 weeks gestation, the 2018 WHO guidelines recommend the use of 200 mg mifepristone administered orally, followed one to two days later by 800 micrograms misoprostol administered vaginally, sublingually or buccally. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours (strong recommendation, moderate certainty evidence). For the medical management of induced abortion at ≥ 12 weeks of gestation, the 2018 WHO guidelines suggest the use of 200 mg mifepristone administered orally, followed one to two days later by repeat doses of 400 micrograms misoprostol administered vaginally, sublingually or buccally every three hours. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours (weak, conditional, discretionary or qualified recommendation, moderate certainty evidence).

Disponibilité

Mifepristone and misoprostol, both individually and co-packaged are available globally.

Autres considérations

The Committee noted the large number of letters of support received in relation to this application.

1. Ganatra B, Gerdts C, Rossier C, Johnson BR, Jr., Tuncalp O, Assifi A et al. Global, regional, and subregional classification of abortion s by safety, 2010-14: estimates from a Bayesian hierarchical model. Lancet. 2017;390(10110):2372–81.
2. Singh S, Maddow-Zimet I. Facility-based treatment for medical complications resulting from unsafe pregnancy termination in the d eveloping world, 2012: a review of evidence from 26 countries. BJOG. 2016;123(9):1489–98.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. Lanc et Glob Health. 2014;2(6):e323–33.
4. The selection and use of essential medicines. Report of the WHO Expert Committee, 2005 (including the 14th Model List of Essen tial Medicines) (WHO Technical Report Series, No. 933). Geneva: World Health Organization; 2005.
5. Medical management of abortion. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/h andle/10665/278968/9789241550406-eng.pdf?ua=1, accessed 29 September 2019.
6. Safe abortion: technical and policy guidance for health systems. 2nd edition. Geneva, World Health Organization. 2012. Available f rom: https://apps.who.int/iris/bitstream/handle/10665/70914/9789241548434_eng.pdf?sequence=1, accessed 29 September 20

19.
7. Health worker roles in providing safe abortion care and post-abortion contraception. Geneva, World Health Organization. 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/181041/9789241549264_eng.pdf?sequence=1, accessed 29 September 2019.
8. Clinical practice handbook of safe abortion. Geneva, World Health Organization. 2014. Available from https://apps.who.int/iris/bitstream/handle/10665/97415/9789241548717_eng.pdf?sequence=1, accessed 29 September 2019.
9. Sjostrom S, Dragoman M, Fonhus MS, Ganatra B, Gemzell-Danielsson K. Effectiveness, safety, and acceptability of first-trimester medical termination of pregnancy performed by non-doctor providers: a systematic review. BJOG. 2017;124(13):1928–40.
10. Clinical updates in reproductive health. Chapel Hill: Ipas; 2019. Available from https://www.ipas.org/resources/clinical-updates-in-reproductive-health, accessed 29 September 2019.
11. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011(1):CD005216.
12. Abubeker FK, Kim CR, Lavelanet A. Medical termination of pregnancy in early first trimester(≤ 63 days): a systematic review. [Evidence synthesis for a WHO guideline]. 2018 (unpublished).
13. Ganatra B. Health worker roles in safe abortion care and post-abortion contraception. Lancet Glob Health. 2015;3(9):e512–3.
14. Glenton C, Sorhaindo AM, Ganatra B, Lewin S. Implementation considerations when expanding health worker roles to include safe abortion care: a five-country case study synthesis. BMC Public Health. 2017;17(1):730.
15. Gupta P, Iyengar SD, Ganatra B, Johnston HB, Iyengar K. Can community health workers play a greater role in increasing access to medical abortion services? A qualitative study. BMC Womens Health. 2017;17(1):37.
16. Barnard S, Kim C, Park MH, Ngo TD. Doctors or mid-level providers for abortion. Cochrane Database Syst Rev. 2015(7):CD011242.
17. Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A et al. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ. 2015;93(4):249–58.
18. Johnson BR, Jr., Maksutova E, Boobekova A, Davletova A, Kazakbaeva C, Kondrateva Y et al. Provision of medical abortion by mid level healthcare providers in Kyrgyzstan: testing an intervention to expand safe abortion services to underserved rural and periurban areas. Contraception. 2018;97(2):160–6.
19. Raymond EG, Blanchard K, Blumenthal PD, Cleland K, Foster AM, Gold M et al. Sixteen Years of Overregulation: Time to Unburden Mifeprex. N Engl J Med. 2017;376(8):790–4.
20. Mifeprex product label, revised March 2016. Silver Spring: U.S. Food and Drug Administration; 2016. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf, accessed 29 September 2019.
21. Winikoff B, Sheldon W. Use of medicines changing the face of abortion. Int Perspect Sex Reprod Health. 2012;38(3):164–6.
22. Kapp N, Blanchard K, Coast E, Ganatra B, Harries J, Footman K et al. Developing a forward-looking agenda and methodologies for research of self-use of medical abortion. Contraception. 2018;97(2):184–8.