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Ohio Policy Evaluation Network

MEDICATION ABORTION AND REMS

BACKGROUND *Last updated: 3/25/22*

Medication abortion consists of a two-pill regimen: mifepristone, followed within 48 hours by misoprostol. The protocol is approved by the Food and Drug Administration (FDA) up to 10 weeks gestation and is extremely safe and effective: "a pregnancy is terminated successfully 99.6% of the time using medication abortion, with a 0.4% risk of major complications, and an associated mortality rate of less than 0.001 percent (0.00064%).[1]

However, the first pill in the regimen, mifepristone, is subject to strict regulation. Mifepristone received FDA approval under the brand name Mifeprex in 2000. In 2019, the FDA approved generic mifepristone. Since its initial FDA approval in 2000, mifepristone has been regulated in ways that impede access to medication abortion. Mifepristone is currently regulated under a Risk Evaluation and Mitigation Strategy (REMS), a safety protocol that can be required by the FDA in addition to the standard safety measures.

RISK EVALUATION AND MITIGATION STRATEGY

The purpose of REMS is to ensure a mode of drug delivery that supports safe use of the drug and minimizes patient risk. The FDA will institute a REMS in exceptional circumstances: when a drug is potentially highly beneficial but carries the risk of serious side effects. A REMS is designed to guard against dangers that are so severe that "without a REMS, these medications would not be approved or would be withdrawn from the market because of known or potential serious risks."[2] In fact, as of June 14, 2021, only 61 medications are subject to a REMS.[3]

The FDA is statutorily required to consider six factors when determining whether a REMS is necessary: (1) size of target population, (2) seriousness of disease or condition, (3) expected benefit of the drug, (4) duration of treatment, (5) seriousness and incidence of known or potential adverse events, and (6) whether the drug is a new molecular entity (21 U.S.C. §355(a)(1)). The relative significance given to each factor is case-specific.

A REMS is comprised of an overall risk mitigation goal plus any information to be communicated (to patients or providers) or action to be taken in service of the goal. When a REMS requires specific actions, they are referred to as Elements to Assure Safe Use (ETASU). A REMS with ETASU may include any of the following requirements: (1) **prescribers have particular training or experience, or are specially certified**; (2) pharmacies, practitioners, or health care settings that dispense the drug are specially certified; (3) **the drug be dispensed to patients only in certain health care settings**; (4) **the drug be dispensed to patients with evidence or other documentation of safe-use conditions**; (5) each patient using the drug be subject to certain monitoring; (6) each patient using the drug be enrolled in a registry.[4] (Bold type indicates elements required under the mifepristone REMS.) When determining what the elements of a REMS will be, the FDA considers both burden on the health care delivery system and patient access.[5]

THE MIFEPRISTONE REMS

The REMS system was formally established in the 2007 amendments to the Food Drug and Cosmetic Act (21 U.S.C. §355-1). Therefore, when mifepristone initially received FDA approval in 2000, it was not under a REMS yet, since REMS did not exist. However, mifepristone was already subject to substantively similar risk regulation called "restrictions to assure safe use" (21 C.F.R. §314.520). The 2007 Amendments provided that any drugs already subject to "restrictions to assure safe use" would be deemed to be under a REMS; thus, mifepristone was automatically brought under the REMS framework when the Amendments took effect.[6] The Mifeprex REMS received official approval in 2011 and was modified in 2016. It was updated in 2019 to account for the approval of generic mifepristone, but in all other respects the 2016 REMS remains current today.

Goal

The goal of the mifepristone REMS is to "mitigate the risk of serious complications associated with mifepristone by: (a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program; (b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber; (c) Informing patients about the risk of serious complications associated with mifepristone.[3]"

ETASU

First, providers who dispense mifepristone must be certified by the drug sponsor. In order to become certified, prescribers must review the Prescribing Information[7] and complete a Prescriber Agreement form. The form certifies that the provider will follow the specific prescribing guidelines set out in the REMS and that they are able to accurately date pregnancy gestation, diagnose ectopic pregnancy, ensure patient access to facilities that provide blood transfusion and resuscitation, and provide surgical intervention for incomplete abortion or severe bleeding *or* plan for such care provision.[8] The REMS guidelines require the provider to review the Patient Agreement form[9] with the patient, sign and obtain the patient's signature on the form, provide the patient with a copy of the form, and place a copy in the patient's medical record. The provider must also provide the patient with a copy of the Medication Guide (a handout provided with the drug that includes safety information for patients). The provider must also record the serial number of the mifepristone package in the patient's medical record and report any deaths to the drug manufacturer. Drug sponsors must ensure that any provider prescribing mifepristone has been certified, and de-certify any who do not comply with the guidelines.

Second, mifepristone can only be dispensed at clinics, medical offices, or hospitals; the REMS specifies that it cannot be dispensed at retail pharmacies.[10]

Third, the REMS requires documentation of a "safe use condition," in this case the Patient Agreement form. The form is given to the patient by the provider, as reviewed above. Patients must sign the form, indicating that they have received counseling on the risks of mifepristone, and that they have read and been provided a copy of the form.

BARRIERS POSED BY THE MIFEPRISTONE REMS

Together, the requirements that the patient receive mifepristone in specific settings after signing the Patient Agreement form create an in-person requirement that limits access. Mifepristone can be safely provided via telemedicine protocols in which a patient never has to present in a clinic.[11] Allowing patients to access medication abortion completely from home would open up this type of care to people who currently face some of the biggest barriers to abortion access, particularly rural and low-income folks.

The prescriber certification requirement limits the pool of potential providers to those who are aware of and willing to go through the certification process. For example, a gynecologist who does not ordinarily perform abortions might see a patient who wants an abortion. For any other medication not subject to certification requirements, the physician could simply prescribe the necessary medication, even if they have never done so before. For mifepristone, instead of writing a prescription right then and there when the patient is in the office, the provider must refer them to an abortion clinic, necessitating at least one more appointment (depending on state waiting period laws), travel to another location, and delay in accessing the patient's desired care.

WHY IS MIFEPRISTONE STILL UNDER A REMS?

Reproductive health researchers,[12] the American College of Obstetricians and Gynecologists,[13] American Medical Association,[14] and American Academy of Family Physicians[15] have publicly taken the position that the REMS, in its entirety, is medically unnecessary and should be removed. Even the former FDA Commissioner who served when Mifeprex was initially approved has publicly called to lift the REMS.[16]

Mifepristone is safe.

Under the FDA's own terms, medications with similar risk profiles should be regulated similarly. When considering burdens on patient access, the FDA "takes into account existing REMS elements for other drugs with similar risks."[17] However, the FDA has approved mifepristone for daily use in patients with Cushing's Syndrome (brand name Korlym), at a higher dose than as an abortifacient (300mg vs 200mg), without a REMS. FDA approval of Korlym without a REMS but Mifeprex/generic mifepristone with a REMS is perhaps the clearest example of how the mifepristone REMS is not medically necessary.

The REMS is not responsive to the risks that mifepristone does pose.

Not only is the risk profile of mifepristone not severe enough to justify the REMS, but the REMS requirements are not even responsive to the risks that mifepristone does pose. As an example of the typical type of risk that might require a REMS, the FDA REMS homepage describes the injectable anti-psychotic Zyprexa Relprevv.[18] In <1% of cases, serious side effects can present within three hours of injection, including sedation, coma, and delirium. Therefore, the Zyprexa Relprevv REMS requires that the injection be administered in a clinical facility capable of monitoring patients for three hours after injection and providing care if necessary. Although the absolute risk is small, the potential consequences are severe enough to merit a special protocol, which is logically tied to the possible adverse outcomes. Contrast this with the mifepristone REMS, which requires the patient to receive the drug in person, but neither makes them take it in the presence of the provider, nor be monitored for the period in which side effects may arise. Indeed, adverse events, which are extremely rare, do not occur until hours or even days after the patient has taken the mifepristone. At this point, it is difficult to see the utility of having been in the physical presence of a provider a day or two earlier. (It is worth noting that the observation requirement makes particular sense for Zyprexa Relprevv, because potential side effects themselves—delirium, coma—may make it difficult or impossible for patients to identify the issue and seek care on their own, while potential side effects of mifepristone—heavy bleeding, infection—do not.) Unlike Zyprexa Relprevv, the mifepristone in-person dispensing requirement is not clearly responsive to the actual risks of the medication: the REMS does not even serve the goals it sets for itself.

CURRENT REMS REVIEW

On May 7, 2021, the FDA announced a full review of the mifepristone REMS. In December 2021, the FDA announced that it would lift the in-person dispensing requirement for mifepristone but left the other REMS requirements in place. The FDA has not yet announced an effective date for this permanent change[19].

Pre-COVID-19

On October 3, 2017 ACLU and ACLU of Hawaii sued FDA on behalf of a private physician, Society of Family Planning, California Academy of Family Physicians, and Pharmacists Planning Services, Inc. The lawsuit challenged the REMS in its entirety as unconstitutional, or in the alternative, a violation of the Administrative Procedure Act. *Chelius v. Azar*, No. 1:17-cv-00493 (D. Haw. Oct. 3, 2017). This litigation is ongoing but currently on hold as a result of the FDA's recent action.

COVID-19 Challenge

Lawmakers[19] and state Attorneys General[20] advocated for lifting the in-person requirements during COVID; over 500 providers, researchers, and medical and advocacy organizations signed onto an April 2020 letter urging the Director of the Center for Drug Evaluation and Research (CDER) to modify the REMS during COVID.[21]

On May 27, 2020, the American College of Obstetricians and Gynecologists, the New York Academy of Family Physicians, and SisterSong Women of Color Reproductive Justice Collective sued to lift the REMS in-person requirements for the duration of the COVID-19 pandemic. They asked for an injunction to stop FDA from enforcing the in-person requirements. The lawsuit did not implicate state telemedicine laws, so mifepristone provision in states that had already prohibited telemedicine for abortion would be unaffected. On July 13, 2020, a federal district court judge in Maryland granted the injunction, suspending certain elements of the REMS until 30 days after the Department of Health and Human Services (HHS) declares an end to the national public health state of emergency. Under the injunction, (1) certified prescribers can send mifepristone by mail, (2) prescribers can mail the Patient Agreement form to the patient, and (3) patients can sign the Patient Agreement form remotely. After a series of appeals, the Supreme Court ultimately dissolved the injunction on January 12, 2021. On April 12, 2021, the Biden Administration announced that FDA would not be enforcing the in-person requirements for the duration of the pandemic.

ENDNOTES

1 "The Availability and Use of Medication Abortion", KFF (2020), https://www.kff.org/womens-health-policy/fact-sheet/the-availability-and-use-of-medication-abortion/.

2 Center for Drug Evaluation and Research, Frequently Asked Questions (FAQs) about REMS, FDA (2018), https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems.and are comprised of information communicated to and/or required activities to be undertaken by one or more participants (i.e., healthcare provider, pharmacists, patients

3 U.S. Food & Drug Administration, Approved Risk Evaluation and Mitigation Strategies (REMS), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (last visited Dec 5, 2020).

4 21 U.S.C. §355-1(f)(3).

5 REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary, (2019), https://www.fda.gov/media/100307/download.

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7 Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf

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12 Mifeprex REMS Study Group, Sixteen Years of Overregulation: Time to Unburden Mifeprex, 376 N. Engl. J. Med. 790–794 (2017), https://doi.org/10.1056/NEJMsb1612526 (last visited Dec 10, 2020).2016, the Food and Drug Administration (FDA

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15 American Academy of Family Physicians, Resolution No. 506 (Co-Sponsored C) - Removing REMS Categorization on Mifepristone (2018), https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf; Michael L. Munger & American Academy of Family Physicians, Letter to Acting Commissioner Sharpless (2019), https://www.aafp.org/dam/AAFP/documents/advocacy/prevention/women/LT-FDA-MifepristoneREMS-062019.pdf.

16 Jane E. Henney & Helene D. Gayle, Time to Reevaluate U.S. Mifepristone Restrictions, 381 N. Engl. J. Med. 597–598 (2019), https://doi.org/10.1056/NEJMp1908305 (last visited Dec 10, 2020).

17 REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary, supra note 5 at 9.

18 Center for Drug Evaluation and, Risk Evaluation and Mitigation Strategies | REMS, FDA (2019), https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems.

19 https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex

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To cite this document: Serpico, Jaclyn and the Ohio Policy Evaluation Network. Medication Abortion and REMS. Fact sheet. July 2021.