

SOUNDING BOARD

Sixteen Years of Overregulation: Time to Unburden Mifeprax

Mifeprax REMS Study Group

On March 29, 2016, the Food and Drug Administration (FDA) approved an updated label for Mifeprax (mifepristone 200-mg tablets, Danco Laboratories), the product that is commonly used in the United States in combination with misoprostol to induce a medical abortion. The changes made to the label were sweeping: they included a more effective dosing regimen containing less mifepristone and more misoprostol, expansion of the gestational limit for treatment from 49 to 70 days, omission of the recommendation for in-person follow-up, removal of language indicating that the prescriber must be a physician, and elimination of the requirement to report nonfatal adverse events. These revisions were supported by extensive data about mifepristone that have been accumulated since the FDA first approved the drug in 2000.¹⁻⁷ Professional guidelines for medical abortion had already incorporated many of the new procedures,⁸⁻¹⁰ and thus the FDA's action brought the drug label into line with current standard practice.

The new label will undoubtedly have substantial benefits. Because the label now conforms with scientific evidence, it will reduce confusion among women, providers, and policymakers about the appropriate use of the drug. Moreover, it is expected to make abortion less expensive, more convenient, and more widely available in the handful of states where legislatures have enacted laws requiring adherence to the FDA-approved Mifeprax label.¹¹

We suggest, however, that in merely updating the label, the FDA did not go far enough: the distribution of Mifeprax remains substantially and unnecessarily encumbered by a Risk Evaluation and Mitigation Strategy (REMS), which was left fundamentally unchanged.

A REMS is a set of restrictions beyond the label that the FDA may impose under the authority of the federal Food, Drug, and Cosmetic Act (FDCA) when necessary to ensure that the benefits of a drug outweigh its risks.^{12,13} REMS programs are

intended for drugs that are known or suspected to cause serious adverse effects that cannot be mitigated simply by the label instructions. The FDCA includes six factors that the FDA should consider when deciding whether to require a REMS, including the benefits and risks of the drug, the duration of treatment, the number of expected users, and the background risk of adverse events in the population (see Box). Each REMS is customized to address the specific risks of a given drug. The REMS for clozapine, which is indicated for the treatment of schizophrenia, is illustrative: because the drug can cause severe neutropenia, its REMS requires, among other measures, that pharmacists verify that each patient has had a recent neutrophil count before dispensing the drug.¹⁴ At this time, 74¹² of the approximately 1750 prescription drug and therapeutic biologic active ingredients that have been approved by FDA and marketed in the United States¹⁵ have REMS programs.

The core of the Mifeprax REMS is three provisions designated as “elements to assure safe use.”¹⁶ First, the drug may be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber; it may not be sold in retail pharmacies. Second, to prescribe the drug, a health care provider must become “certified” by completing and sending a form to the drug distributor attesting that he or she can assess pregnancy duration, diagnose ectopic pregnancy, and provide surgical intervention if needed, either personally or by referral. Third, each woman taking Mifeprax must be given an FDA-approved medication guide and sign an FDA-approved patient agreement that summarizes the use instructions specified in the label and the potential risks of the drug. Whereas drug labels are generally not binding for individual clinicians¹⁷ — misoprostol, for example, is approved for the prevention of gastric ulcers but is legally and widely used off-label for gynecologic purposes,

Excerpts from the Food, Drug, and Cosmetic Act Relevant to Risk Evaluation and Mitigation Strategies.***a. Submission of proposed strategy**

1. Initial approval

If the Secretary . . . determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug, and informs the person who submits such application of such determination, then such person shall submit to the Secretary as part of such application a proposed risk evaluation and mitigation strategy. In making such a determination, the Secretary shall consider the following factors:

- A. The estimated size of the population likely to use the drug involved.
- B. The seriousness of the disease or condition that is to be treated with the drug.
- C. The expected benefit of the drug with respect to such disease or condition.
- D. The expected or actual duration of treatment with the drug.
- E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- F. Whether the drug is a new molecular entity.
- G. Assuring access and minimizing burden.

. . .

f. Providing safe access for patients to drugs with known serious risks that would otherwise be unavailable

1. Allowing safe access to drugs with known serious risks

The Secretary . . . may require that the risk evaluation and mitigation strategy for a drug include such elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness, if the Secretary determines that —

- A. the drug, which has been shown to be effective, but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements are required as part of such strategy to mitigate a specific serious risk listed in the labeling of the drug; and
- B. for a drug initially approved without elements to assure safe use, other elements . . . are not sufficient to mitigate such serious risk.

2. Assuring access and minimizing burden

Such elements to assure safe use . . . shall:

- A. be commensurate with the specific serious risk listed in the labeling of the drug;
- B. within 30 days of the date on which any element . . . is imposed, be posted publicly by the Secretary [of Health] with an explanation of how such elements will mitigate the observed safety risk;
- C. considering such risk, not be unduly burdensome on patient access to the drug, considering in particular —
 - i. patients with serious or life-threatening diseases or conditions; and
 - ii. patients who have difficulty accessing health care (such as patients in rural or medically underserved areas); and
- D. to the extent practicable, so as to minimize the burden on the health care delivery system —
 - i. conform with elements to assure safe use for other drugs with similar, serious risks; and
 - ii. be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

* Information is quoted from the Food Drug and Cosmetic Act, Section 505-1, codified at 21 U.S.C. §355-1.

such as labor induction¹⁸ — compliance with a REMS is mandatory and consequently has a nationwide effect.

When Mifeprex was first approved 16 years ago, documented experience with its use outside a research context was minimal, and the restrictions to minimize potential harm were perhaps understandable. Since then, however, its effectiveness and safety have been definitively established. To date, 19 deaths have been reported to the FDA among the more than 3 million women in the United States who have used Mifeprex (Long A, Danco Laboratories; personal communication); the

estimated Mifeprex-associated mortality rate is thus 0.00063%. In contrast, the background risk of pregnancy-related death among pregnant women in the United States who do not have abortions and instead proceed to live birth is approximately 0.009%, which is 14 times higher.¹⁹ Studies that together included more than 423,000 women around the world who had a medical abortion have reported that the rates of nonfatal serious adverse events after mifepristone use, such as hospital admission, blood transfusion, or serious infection, range from 0.01 to 0.7%, and these events are almost always treatable without permanent sequelae.

Side effects such as bleeding, cramping, fever, and chills are typically minor and transient.² This reassuring safety record and the fact that each woman using Mifeprex receives only a single pill, which virtually eliminates the potential for substantial misuse, suggests that Mifeprex no longer fits the expected profile of a drug that requires a REMS.

Indeed, in our view, the Mifeprex REMS is inconsistent with the express requirements of the FDCA. The law states that a REMS may include the elements to assure safe use only if the “inherent toxicity or potential harmfulness” of the drug is such that no other means are available to mitigate a “specific serious risk” listed on the label. If included, the elements must be “commensurate” with this risk and must include an explanation of how the elements will mitigate this risk. In addition, the elements must not unduly burden either patient access to the drug — especially among patients with serious medical conditions and patients in medically underserved areas — or the health care system (see Box).

The Mifeprex elements do not meet these specifications. Mifepristone is not inherently toxic or harmful to the woman using it. The notion that the elements are essential to ensure that its benefits outweigh its risks has no basis in evidence; on the contrary, other countries that have not instituted regulations similar to the REMS have not encountered substantial safety problems. One or both of the two serious risks described on the Mifeprex label — atypical infection and prolonged heavy vaginal bleeding — also may occur after many other common obstetrical and gynecologic procedures, including vaginal delivery, medical and surgical management of miscarriage, and insertion of intrauterine devices. All these procedures are routinely performed without federally mandated provider certification, signed patient agreements, or venue limitations, and yet they are generally considered to be acceptably safe. In this context, a rationale for singling out Mifeprex as needing such measures to ensure safety is lacking, and the Mifeprex elements can hardly be justified as “commensurate” with the risks.

Similarly in conflict with the law, the Mifeprex REMS provides no explanation as to how the elements to assure safe use — in particular, the restriction on dispensing sites — could possibly have any effect on the risks of infection or bleeding. The new Mifeprex label permits a woman to take the drug after leaving the dispensing facility, and

the pharmacologic effects do not begin for hours after ingestion. If a serious complication were to occur, the location where the woman had obtained the tablets would be entirely irrelevant to her clinical outcome. In fact, recent research has shown that allowing each woman who has a medical abortion to take the mifepristone in the place of her choosing is safe and is preferred by many women.²⁰⁻²²

The Mifeprex elements to assure safe use plainly impede women’s access to the drug.¹¹ For example, the prohibition on sale at retail pharmacies and the provider certification requirement mean that a qualified clinician who has not completed the certification process and arranged to stock the drug in his or her office cannot provide timely medical abortion care to a woman who presents unexpectedly. Consequently, treatment of such a patient would be delayed, increasing cost and inconvenience and, if the delay is substantial, possibly even medical risk. The elements also complicate the provision of medical abortion through telemedicine,²³ which has proved valuable in improving access in rural areas.²⁴ More generally, the expense and hassle of maintaining drug inventories as well as reluctance to be included on a list of certified abortion providers — understandable, given the long history of harassment and violence²⁵ — may discourage some otherwise willing clinicians from offering medical abortion at all. Considering the severe shortage of abortion providers in many parts of the United States and the long distances that many women must travel to obtain abortion services,²⁶ we contend that any barrier to access that has no demonstrated benefit is excessive.

Finally, the Mifeprex elements to assure safe use violate the statutory requirement to minimize the burden on the health care delivery system. In particular, the elements are not compatible with established drug-distribution systems; instead, the Mifeprex distributor has had to set up an onerous and costly infrastructure, used only for this one drug, to enable clinicians to submit certification forms and order supplies. This process certainly does not conform to the distribution system for other drugs with similar serious risks. Anticoagulants can cause major bleeding at numerous anatomic sites, including the vagina,²⁷⁻²⁹ and phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction are estimated to be associated with death in up to 0.004% of users,³⁰ and yet

these drugs do not have REMS programs. Antibiotics, antihypertensive agents, and insulin also can induce immediate serious or fatal reactions shortly after use, but most of these also are not restricted by REMS. In addition, the Mifeprex elements may impede the development of potentially cheaper, generic mifepristone products for abortion by requiring any generic developer either to negotiate a shared distribution system with the distributor of Mifeprex or to set up a separate, parallel system.

Given the data and experience that have been accumulated since the initial FDA approval, the Mifeprex REMS no longer makes clinical sense. The provider certification criteria can technically be met by any health care professional with the ability to read an ultrasound report and familiarity with emergency services, and thus the certification process itself — which is a self-certification without any validation component — is, in essence, an empty formality. Serious complications of mifepristone treatment are uncommon and are very familiar to clinicians who provide care to women of reproductive age; these risks should be manageable through routine labeling and standard clinical counseling. And abortion providers certainly can evaluate patients and prescribe mifepristone without having tablets physically present in their offices.

Medical abortion is a key component of women's health care because it enables effective, safe, private pregnancy termination when surgical abortion is unavailable, clinically contraindicated, or personally undesirable. Mifepristone is currently the only drug approved for medical abortion in the United States, and more than a third of women who present for abortion within the first 8 weeks of gestation now choose to use it. Some evidence suggests that access to this drug can reduce the demand for induced abortion in the second trimester.³¹ The Mifeprex REMS impedes the provision of Mifeprex without offering any demonstrated or even reasonably likely advantage. We recommend that the REMS be expeditiously withdrawn.

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