CONFIDENTIAL*

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March 11, 2022

(b)(6)/PPI

Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

Re: NDA 20-687, eCTD Sequence No.16
MIFEPREX® (mifepristone) tablets, 200 mg

Type A Meeting Request and Background Materials in Response to REMS Modification Notification Dated December 16 re Mifepristone SSS REMS Program

Dear (b)(6)/PPI

Reference is made to New Drug Application 20-687 for MIFEPREX® (mifepristone) tablets, 200 mg submitted under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Reference is also made to the Single Shared System Risk Evaluation and Mitigation Strategy (SSS REMS) approved on April 11, 2019 for MIFEPREX® and GenBioPro's mifepristone (ANDA 091178) and the REMS Modification Notification dated December 16, 2021 received by both Danco and GenBioPro.

Following receipt of the REMS Modification Notification from the FDA dated December 16, 2021, Danco has been working together with GenBioPro to prepare questions for the FDA with a view to obtaining guidance regarding certain key elements included in that Notification. These questions together with background information have been included in a Type A Meeting Request seeking written responses only (WRO) (see attached).

Given that the FDA is requesting submission of a proposed REMS modification within 120 days of December 16, 2021, we request that FDA responds to the questions in the Type A Meeting Request (WRO) as soon as possible.

Sincerely

(b)(4)/TS-CI; (b)(6)/PPI

Attachment: Type A Meeting Request

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* This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61.** Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, LLC requests immediate notification and an opportunity for consultation in accordance with **21 C.F.R. 20.45.** Contact telephone number is (b)(4)/TS-CI; (b)(6)/PPI

Requirements. The pharmacy, through its authorized representative, certifies that it will implement necessary actions to ensure the following:

i) Dispense mifepristone only under prescriptions issued by or under the authority of a certified prescriber (see below for contemplated verification and questions on certified prescribers);

ii) No transfer of mifepristone other than to a patient per above, a certified prescriber, another certified pharmacy, or for returns or destruction;

iii) Communicate any reported deaths of mifepristone users to the prescriber;

iv) The Medication Guide is available to patients;

v) Maintain records of the above and accept audits; and

vi) Protect the confidentiality and privacy of providers and patients.

***Rationale*:** The above proposed requirements should be sufficient to ensure those goals are met. Under the REMS, counseling and other elements of safe use are conducted by or under the supervision of the certified prescriber. Having the pharmacy report deaths to the certified prescriber ensures reporting (as certified prescribers are required to report to the manufacturer) while avoiding duplication of reports or compromising patient confidentiality.

d) **Pharmacy Verification of Prescriber Certification/REMS Compliance and Protection of Prescriber Safety and Confidentiality.**

As the Agency understands, providing medical abortion with mifepristone may expose prescribers to extreme risks to their safety that are different from any other drug product. The ever-present risk of anti-abortion violence creates material security and confidentiality risks for mifepristone prescribers, distributers, pharmacies, and patients. Accordingly, care must be taken to ensure that any modification to the Mifepristone REMS Program does not create a risk of unauthorized disclosure of identifying information about any of these stakeholders. (b)(4)/TS-CI [redacted]. Any apparent or potential risk would cause many prescribers—including existing prescribers—to refrain from becoming or remaining mifepristone prescribers.

Nonetheless, the Sponsors assume that, if mifepristone is to be dispensed by pharmacies, the REMS must include a process by which a pharmacy first confirms that the prescriber is specially certified. Currently the prescriber verification process is handled by the distributors for each product, each of which receives a

June 21, 2022

Robert Califf, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: U.S. Food and Drug Administration actions related to mifepristone

Dear Dr. Califf:

On behalf of the American College of Obstetricians and Gynecologists (ACOG), representing more than 60,000 physicians and partners dedicated to advancing women's health and individuals seeking obstetric and gynecologic care, and the American Medical Association, we write to express our appreciation for the support demonstrated by the U.S. Food and Drug Administration (FDA) in response to the needs of individuals seeking reproductive care. Respectfully, we request that additional actions are taken to improve access to quality women's health care. In anticipation of the crisis to abortion access that is expected to follow the United States Supreme Court's decision in the *Dobbs v. Jackson Women's Health Organization* case, we strongly urge you to prioritize the following evidence-based decisions that will increase access to mifepristone:

- Reconsider the implementation of the Risk Evaluation and Mitigation Strategies (REMS) and Elements to Assure Safe Use (ETASU) requirements for mifepristone and ensure the process does not add unnecessary and unmitigated burdens for physicians, patients, and pharmacies; and
- Explicitly preempt state laws relating to mifepristone that are not evidence-based, that interfere with the medically necessary and appropriate use of a safe and effective drug, and that frustrate the FDA's regulatory decisions relating to mifepristone, and that have inconsistent policies and laws restricting access to mifepristone.

Mifepristone is Safe and Effective

Mifepristone is a safe, effective, and important component of treatment and management for early pregnancy loss (i.e., spontaneous abortion, miscarriage, missed abortion) and induced abortion. Mifepristone has been used by over 3 million women in the United States since FDA approval in 2000, and robust evidence exists regarding the safety of mifepristone for medication-induced abortion.[1,2,3,4]

Early pregnancy loss is common, occurring in 10% of all clinically recognized pregnancies and affects approximately 1 million women in the U.S. annually.[5,6] Recent evidence demonstrates that mifepristone significantly improves the safe and effective medical management of early pregnancy loss when taken as part of a two-medication regimen.[7,8] A 2018 randomized controlled trial demonstrated that people who received mifepristone in addition to misoprostol experienced increased rates of complete expulsion and required fewer procedures compared to those who received misoprostol alone.[9] Therefore, we ask that the FDA modify the mifepristone label indicating that mifepristone is approved for the use of miscarriage management.

As referenced in ACOG clinical guidance, the evidence supports medication abortion as a safe and effective method of providing abortion care.[10] Barriers to accessing mifepristone do not make care safer, are not based on medical evidence, and create barriers to patient access to essential reproductive health care.[11, 12] Abortion care is time-sensitive: delays in care increase risk to patients and potentially results in an abortion being completely inaccessible.[13] Research conducted during the COVID-19 pandemic demonstrates that when enforcement of the in-person dispensing requirement for mifepristone was suspended, abortion through telehealth contact and mailed medications was safe.[14]

According to reaffirmed ACOG guidance, second-trimester abortion is safely accomplished through medical induction or medical abortion, especially when compared with other methods.[15] Mifepristone followed in 24–48 hours by misoprostol is the most effective regimen for second-trimester medical abortion.[16] In fact, that regimen is up to 91% successful within 24 hours of initiation of misoprostol, and outcomes include a significantly shorter induction interval and fewer adverse effects than misoprostol alone.[17]

FDA Preemption of State Laws that Restrict Access to Mifepristone

There are currently nineteen states that require a physician to be present upon delivery of mifepristone; two states have made it illegal to use mifepristone at earlier gestation ages than the label allows.[18] Neither of these state restrictions are evidence-based.

Mifepristone is approved by the FDA to be used with misoprostol for medication abortion through 70 days of gestation.[19,20] In 2016, the FDA expanded the gestational age limit from 49 to 70 days (10 weeks) to better correspond with recently published evidence.[21,22] The 2015 systematic review reported average effectiveness rates of 96.7% in the 8th week, 95.2% in the 9th week, and 93.1% in the 10th week. Subsequently, evidence-based guidelines concluded that mifepristone followed in 24–48 hours by misoprostol is the most effective regimen for second-

trimester medical abortion.[23] Currently, strong evidence supports the use of the mifepristone regimen through 77 days gestation, and multi-center study published in 2022 found that many physicians offer mifepristone up to 77 days.[24,25]

Experts, including ACOG, and the growing body of scientific evidence, demonstrate that the FDA regulations should preempt those state laws and prevent state lawmakers from imposing restrictions that are not evidence-based, that interfere with the medically necessary and appropriate use of a safe and effective drug, that frustrate access to necessary care and are inconsistent with the FDA's regulatory decisions relating to mifepristone.

Revisit or Remove the Risk Evaluation and Mitigation Strategies (REMS) and Elements to Assure Safe Use (ETASU) Requirements for Mifepristone

Recognizing the accomplishments of the FDA in modifying the REMS for mifepristone, we continue to urge the FDA to remove or make further changes to the REMS and ETASU requirements to allow obstetrician–gynecologists and other physicians to deliver the highest quality care for their patients. While the FDA updated the REMS for mifepristone in December 2021, the REMS for mifepristone still requires use of a provider agreement form, a patient agreement form and dispensing from a pharmacy certified by the drug distributors. The agency and manufacturers have not yet defined the pharmacy certification process; however, we are concerned that this unnecessary hurdle could serve as a deterrent to pharmacies' decisions to stock and dispense mifepristone. To increase access to mifepristone, we ask that, at a minimum, the FDA simplify the pharmacy certification process, eliminate the requirement for patients to sign a form to get the drug, lift the requirement that prescribers acquire a certification from the manufacturer, and evaluate adding protections for availability of mifepristone via telehealth.

Failure to Improve Access to Mifepristone Will Threaten to Exacerbate the Maternal Mortality Crisis

The United States leads the developed world in rates of maternal mortality. In 2020, the most recent year for which data is available, there were 23.8 deaths per 100,000 live births, up from 20.1 in 2019.[26] Alarmingly, the maternal mortality rate for Black women was 55.3 deaths per 100,000 live births, 2.9 times the rate for White women, and rates significantly increased for both Black and Hispanic women.[27] The rising maternal mortality rates and persistent racial disparities in maternal outcomes are unacceptable. However, without sufficient access to abortion care, including mifepristone, these figures are certain to climb.

Current data support an association between restricted access to safe and legal abortion and higher rates of maternal morbidity and mortality, with already vulnerable populations experiencing the greatest burden.[28,29,30] At just 0.3 deaths per 100,000 abortions performed at or before 8 weeks, the mortality rate associated with abortion is significantly lower than the mortality rate associated with childbirth.[31] A lack of access to mifepristone will result in more pregnancies, including high-risk pregnancies, which is associated with the much higher maternal mortality rates described above. A recent study estimated a total, nationwide abortion ban would increase pregnancy-related deaths by 7% in the first year and 21% in subsequent years, including a 33% increase for Black people.[32]

Furthermore, research suggests that a lack of abortion access carries the risk of adverse physical outcomes. The harm of mifepristone restrictions is also more pronounced for patients with medical conditions for which a medication abortion may be preferable to uterine aspiration. Such examples include uterine fibroids that significantly distort the cervical canal or uterine cavity, congenital uterine anomalies, or introital scarring related to infibulation.[33] Patients with asthma are candidates for medication abortion because misoprostol does not cause bronchoconstriction and actually acts as a weak bronchodilator.[34] Carrying a pregnancy to term is also associated with mental health conditions. A 2017 study found women who were denied abortions experienced more symptoms of anxiety, lower self-esteem, and lower life satisfaction after one week than their counterparts who obtained abortions.[35] Perinatal depression, which includes major and minor depressive episodes that occur during pregnancy or in the first 12 months after delivery, is one of the most common medical complications during pregnancy and the postpartum period, affecting one in seven.[36] Finally, restrictions on the use of telemedicine have a disproportionate effect on rural people's access to abortion, who are forced to travel substantially greater distances outside of their communities than nonrural women for care.[37]

Thank you for your attention to this critical issue and your continued partnership with us. Your commitment and dedication to advancing women's health and individuals receiving obstetric and gynecologic care is recognized and appreciated. Should you have any questions, please contact Rebecca Lauer, Manager, Federal Affairs, at rlauer@acog.org.

Sincerely,

Maureen G. Phipps, MD

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists

James L. Madara, MD
CEO, Executive Vice President
American Medical Association

cc: The Honorable Joseph R. Biden, Jr.
The Honorable Kamala D. Harris

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The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

A Better Medical Regimen for the Management of Miscarriage

Carolyn L. Westhoff, M.D.

Data from the National Survey of Family Growth suggest that at least 600,000 cases of early pregnancy loss, often called miscarriage, occur before 12 weeks of gestation each year in the United States.[1] The treatment options for a woman with a miscarriage include observation until spontaneous resolution, vacuum aspiration, or medical management with misoprostol.[2] Observation is often slow and always unpredictable, and aspiration is quick and predictable but invasive; the time frame, predictability, and invasiveness of medical management fall somewhere between those of observation and aspiration. The rate of success with a single dose of 800 μg of misoprostol administered vaginally is approximately 90% among women who have pain and bleeding associated with the miscarriage,[3,4] but most early miscarriages are diagnosed before the onset of symptoms. Among women who receive a diagnosis of miscarriage, a single dose of misoprostol is effective within 3 days after administration for only 70%, although by 30 days after misoprostol use, the rate of success reaches 87% among women in whom fetal death has occurred and 79% among women who have an anembryonic gestation.[3,4] The greater rate of success observed 30 days after treatment results from the passage of time and sometimes from a second dose of misoprostol. Slower treatment success is associated with more visits, more ultrasonographic examinations, and more patient anxiety. Medical management with misoprostol substantially reduces the need for an aspiration procedure to complete the abortion, but offering medical management that can result in quicker success would be desirable.

In this issue of the *Journal*, Schreiber et al.[5] report the results of a clinical trial involving 300 women who were confirmed to have a nonviable intrauterine pregnancy (anembryonic gestation or embryonic or fetal death) by 12 weeks of gestation. Participants were randomly assigned to receive pretreatment with 200 mg of mifepristone, administered orally, followed by 800 μg of misoprostol, administered vaginally, approximately 24 hours later, or standard therapy with 800 μg of misoprostol alone, administered vaginally. This regimen of mifepristone plus misoprostol was previously shown to be more effective for induced abortion than misoprostol alone.[3,6] At an average of 3 days after misoprostol treatment, the rate of treatment success (which the authors defined as gestational sac expulsion by the first follow-up visit with one dose of misoprostol and no additional surgical or medical intervention within 30 days after treatment) was 67% with misoprostol alone (a finding consistent with the results of previous studies of misoprostol alone), as compared with 84% with mifepristone pretreatment followed by misoprostol. The number of mifepristone doses needed for one additional treatment success (i.e., the number needed to treat) was 6. By 30 days, 24% of the women who had received misoprostol alone underwent uterine aspiration, as compared with 9% of the women who had received mifepristone pretreatment.

In the group of 149 women who received mifepristone pretreatment, 3 (2.0%) required a blood transfusion and 2 (1.3%) had a pelvic infection; these outcomes were similarly infrequent in the misoprostol-alone group, and the frequency of these outcomes was similar among

the women who underwent uterine aspiration.[3] Side effects were similar in the two treatment groups, with the exception of more vomiting reported among women who received mifepristone pretreatment than among those who received misoprostol alone (27% vs. 15%). These results provide strong evidence that the sequential regimen of mifepristone followed by misoprostol is safe and is superior to misoprostol alone in attaining quick treatment success and avoiding an aspiration procedure. These results support the use of the sequential regimen as the standard of care.

Among the 721 women who met inclusion criteria for the trial, 42% enrolled, a rate that indicates a substantial interest in medical management. Study participants were diverse with respect to geographic region, race and ethnic group, and type of medical insurance; most found the treatments acceptable. On the basis of these results, one might expect as many as half the women with miscarriage to choose medical management with mifepristone plus misoprostol.

This regimen of mifepristone plus misoprostol aligns with patient preferences for quicker treatment success. Although the current report did not include an analysis of cost-effectiveness, quicker treatment success would be expected to reduce costs (for additional office visits, ultrasonographic examinations, and aspiration procedures), as well as to reduce associated inconvenience. Timely availability of sequential treatment with mifepristone and misoprostol is not, however, as simple as it should be. Mifepristone is regulated by the Food and Drug Administration in that it requires a Risk Evaluation and Mitigation Strategy (REMS). REMS restrictions, which are intended for drugs that have been shown to have serious adverse effects, limit drug distribution, but extensive clinical experience with mifepristone indicates that there is no need for such restrictions.[7] The REMS requirement for mifepristone prevents prescription sales in retail pharmacies. Thus, any patient with miscarriage who might prefer this treatment must find a clinician who stocks mifepristone in the office. This restriction places a burden on both women and clinicians that would delay care and surely decrease the use of this safer, more effective treatment regimen.

Medical management should never be the only treatment for women with miscarriage; women who are bleeding heavily and women who prefer surgical management should have prompt access to aspiration. Symptomatic women should be able to undergo aspiration in emergency departments, and asymptomatic women in the office setting. The treatment of miscarriage in the operating room is not cost-effective or convenient and should be rare.[8,9] The trial by Schreiber et al. supports a better approach for women who want medical management for miscarriage. To provide better care for the more than half a million U.S. women with miscarriage each year, we need to work on improving availability of this and other office-based treatments.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Columbia University Medical Center, New York.

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World Health Organization

Medical management of abortion

1.1 Background

Mifepristone and misoprostol in combination or misoprostol alone are the medications generally used to induce abortion and to manage incomplete abortion or intrauterine fetal demise (IUFD).

These medications are increasingly available globally, and they are on the World Health Organization (WHO) List of Essential Medicines *(1)*. Mifepristone is an anti-progestin which binds to progesterone receptors, inhibiting the action of progesterone and hence interfering with the continuation of pregnancy. Treatment regimens entail an initial dose of mifepristone followed by administration of a synthetic prostaglandin analogue, misoprostol, which induces cervical softening and dilation and enhances uterine contractions, which aids in expelling the products of conception *(2,3)*.

Misoprostol is a prostaglandin E1 analogue that can be used either in combination with mifepristone or on its own *(4–6)*. Misoprostol has a wide range of reproductive health applications, including induction of labour, management of spontaneous and induced abortion, and prevention and treatment of postpartum haemorrhage *(7)*. Due to the ease of handling and storing it, as well as its non-invasiveness and proven cost-effectiveness, the use of misoprostol within abortion care – either in combination with mifepristone or alone – offers several advantages. It reduces the need for skilled surgical abortion providers, equipment, sterilization and anaesthesia, while offering a non-invasive and highly acceptable option to pregnant individuals *(8)*. For these reasons, and because it is stable at room temperature within its packaging, misoprostol is particularly useful in low-resource settings *(7)*.

Medical abortion plays a crucial role in providing access to safe, effective and acceptable abortion care. Previous guidance published by WHO, including *Safe abortion: technical and policy guidance for health systems* (2012), provided recommendations for the use of mifepristone and misoprostol in combination or misoprostol alone for the management of medical abortion *(6)*. The 2012 guidance stated that many interventions in medical abortion care, particularly those

Introduction

in early pregnancy, can be provided at the primary care level and on an outpatient basis, which further increases access to care *(6)*. In both high- and low-resource settings, the use of medical methods of abortion have contributed to task shifting and sharing and more efficient use of resources *(9)*. Given the nature of the medical abortion process, it is also possible for individuals to play a role in managing some of the components by themselves, outside of a health-care facility. Another existing WHO guideline, *Health worker roles in providing safe abortion and post-abortion contraception* (2015), recommends that in specific circumstances, individuals may self-manage their mifepristone and/or misoprostol medication without direct supervision of a health-care provider, as well as self-assess the success of the abortion process using pregnancy tests and checklists *(10)* (see Box 1). It should be noted that pregnancy tests used to self-assess the success of the abortion process are low-sensitivity urine pregnancy tests, which are different from those tests commonly used to diagnose pregnancy. Such self-assessment and self-management approaches can be empowering for individuals and help to triage care, leading to a more optimal use of health-care resources.

All individuals who can become pregnant, including women, girls and those with varying gender identities, and who seek medical abortion care should be provided with all of the necessary information to make an informed decision to ensure the promotion of their health and human rights, including sex and gender equality and non-discrimination. With this information, individuals can decide freely and responsibly the number, spacing and timing of their children *(11)*. It is the right of every person, regardless of marital status, to enjoy the benefits of scientific progress and its applications *(11)*.

All individuals who can become pregnant, including women, girls and those with varying gender identities, and who seek medical abortion care should be provided with all of the necessary information to make an informed decision to ensure the promotion of their health and human rights, including sex and gender equality and non-discrimination.

Depending upon the context, unmarried individuals, adolescents, those living in extreme poverty, individuals from ethnic minorities, refugees and other displaced persons, people with disabilities, and those facing violence in the home may be vulnerable to inequitable access to safe abortion services. Adolescents, in particular, are less likely than adults to be able to obtain legal and safe abortions to terminate their pregnancies. Some of the barriers adolescents face include requirements for third party authorizations (including parental consent) and financial constraints (inability to pay the required fees) *(6,12)*. Additional considerations related to the care of adolescents can be found in section 4 (General implementation considerations), and in the WHO adolescent job aid *(13)*.

Where geographic inequities exist, people must travel greater distances for care, thereby raising costs and delaying access *(14)*. Financing mechanisms should ensure equitable access to good-quality services *(15)*. Where individuals are charged fees for abortion, such fees should be matched to their ability to pay,

NATIONAL CENTER FOR HEALTH STATISTICS
Health E-Stats
FEBRUARY 2022

Maternal Mortality Rates in the United States, 2020

by Donna L. Hoyert, Ph.D., Division of Vital Statistics

This report presents maternal mortality rates for 2020 based on data from the National Vital Statistics System. A maternal death is defined by the World Health Organization as, "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes" (1). Maternal mortality rates, which are the number of maternal deaths per 100,000 live births, are shown in this report by age group and race and Hispanic origin.

This report updates a previous one that showed maternal mortality rates for 2018 and 2019 (2). In 2020, 861 women were identified as having died of maternal causes in the United States, compared with 754 in 2019 (3). The maternal mortality rate for 2020 was 23.8 deaths per 100,000 live births compared with a rate of 20.1 in 2019 (Table).

In 2020, the maternal mortality rate for non-Hispanic Black women was 55.3 deaths per 100,000 live births, 2.9 times the rate for non-Hispanic White women (19.1) (Figure 1 and Table). Rates for non-Hispanic Black women were significantly higher than rates for non-Hispanic White and Hispanic women. The increases from 2019 to 2020 for non-Hispanic Black and Hispanic women were significant. The observed increase from 2019 to 2020 for non-Hispanic White women was not significant.

Rates increased with maternal age. Rates in 2020 were 13.8 deaths per 100,000 live births for women under age 25, 22.8 for those aged 25–39, and 107.9 for those aged 40 and over (Figure 2 and Table). The rate for women aged 40 and over was 7.8 times higher than the rate for women under age 25. Differences in the rates between age groups were statistically significant. Among age groups, the increase in the rates between 2019 and 2020 for women aged 25–39 and 40 and over were statistically significant.

Data sources and methods

Data are from the National Vital Statistics System mortality file (4). Consistent with previous reports, the number of maternal deaths does not include all deaths occurring to pregnant or recently pregnant women, but only those deaths with the underlying cause of death assigned to *International Statistical Classification of Diseases, 10th Revision* code numbers A34, O00–O95, and O98–O99. Maternal mortality rates are per 100,000 live births based on data from the National Vital Statistics System natality file. Maternal mortality rates fluctuate from year to year because of the relatively small number of these events, and possibly also due to issues associated with the reporting of maternal deaths on death certificates (3). Efforts to improve data quality are continuous, and these data will continue to be evaluated for possible errors.

References

1. World Health Organization. International statistical classification of diseases and related health problems, 10th revision. 2008 ed. 2009.

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3. Hoyert DL, Miniño AM. Maternal mortality in the United States: Changes in coding, publication, and data release, 2018. National Vital Statistics Reports; vol 69 no 2. Hyattsville, MD: National Center for Health Statistics. 2020.

4. Murphy SL, Kochanek KD, Xu JQ, Arias E. Mortality in the United States, 2020. NCHS Data Brief, no 427. Hyattsville, MD: National Center for Health Statistics. 2021.

Suggested citation

Hoyert DL. Maternal mortality rates in the United States, 2020. NCHS Health E-Stats. 2022. DOI: https://dx.doi.org/10.15620/cdc:113967.

Table. Number of live births, maternal deaths, and maternal mortality rates, by race and Hispanic origin and age: United States, 2018–2020

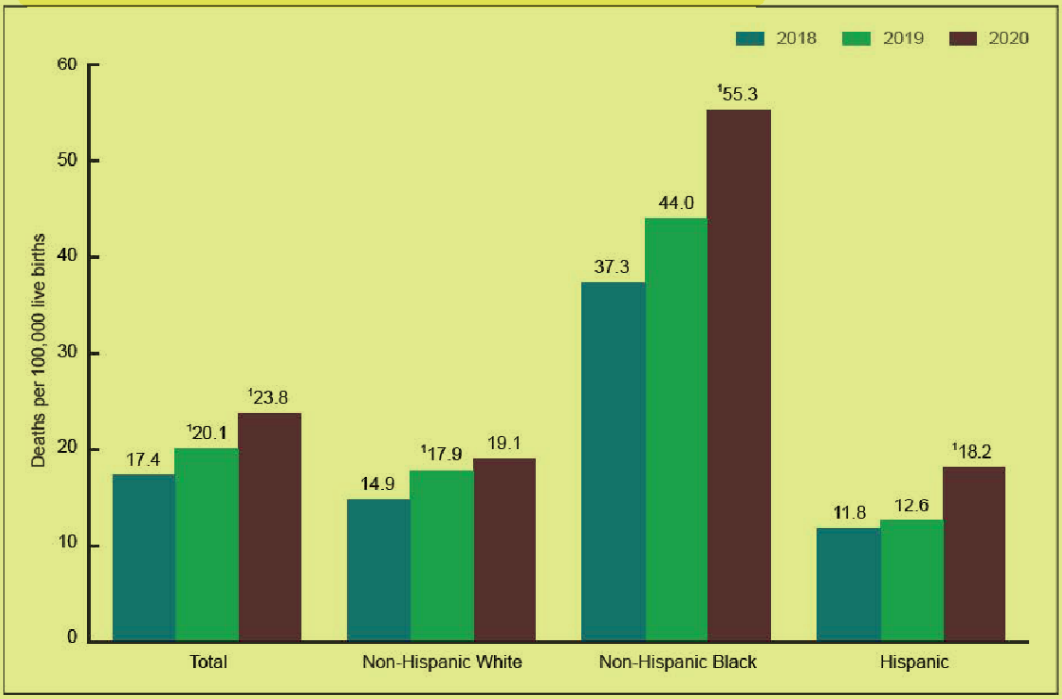
Race and Hispanic origin and age	2018			2019			2020		
	Live births	Maternal deaths	Maternal mortality	Live births	Maternal deaths	Maternal mortality	Live births	Maternal deaths	Maternal mortality
	Number		Rate[1]	Number		Rate[1]	Number		Rate[1]
Total[2]	3,791,712	658	17.4	3,747,540	754	20.1	3,613,647	861	23.8
Under 25	907,782	96	10.6	877,803	111	12.6	825,403	114	13.8
25–39	2,756,974	458	16.6	2,739,976	544	19.9	2,658,445	607	22.8
40 and over	126,956	104	81.9	129,761	98	75.5	129,799	140	107.9
Non-Hispanic White[3]	1,956,413	291	14.9	1,915,912	343	17.9	1,843,432	352	19.1
Under 25	391,829	41	10.5	374,129	49	13.1	348,666	40	11.5
25–39	1,504,888	207	13.8	1,480,595	248	16.8	1,433,839	253	17.6
40 and over	59,696	43	72.0	61,188	46	75.2	60,927	59	96.8
Non-Hispanic Black[3]	552,029	206	37.3	548,075	241	44.0	529,811	293	55.3
Under 25	176,243	27	15.3	169,853	32	18.8	159,541	46	28.8
25–39	358,276	137	38.2	360,206	179	49.7	351,648	198	56.3
40 and over	17,510	42	239.9	18,016	30	166.5	18,622	49	263.1
Hispanic	886,210	105	11.8	886,467	112	12.6	866,713	158	18.2
Under 25	275,553	21	7.6	270,948	23	8.5	258,635	20	7.7
25–39	579,553	72	12.4	584,109	71	12.2	576,690	111	19.2
40 and over	31,104	12	*	31,410	18	*	31,388	27	86.0

* Rate does not meet National Center for Health Statistics standards of reliability.
[1]Maternal mortality rates are deaths per 100,000 live births.
[2]Total includes race and origin groups not shown separately, including women of multiple races and origin not stated.
[3]Race groups are single race.

NOTES: Maternal deaths are those assigned to code numbers A34, O00–O95, and O98–O99 of the *International Classification of Diseases, 10th Revision*. Maternal deaths occur while pregnant or within 42 days of being pregnant.

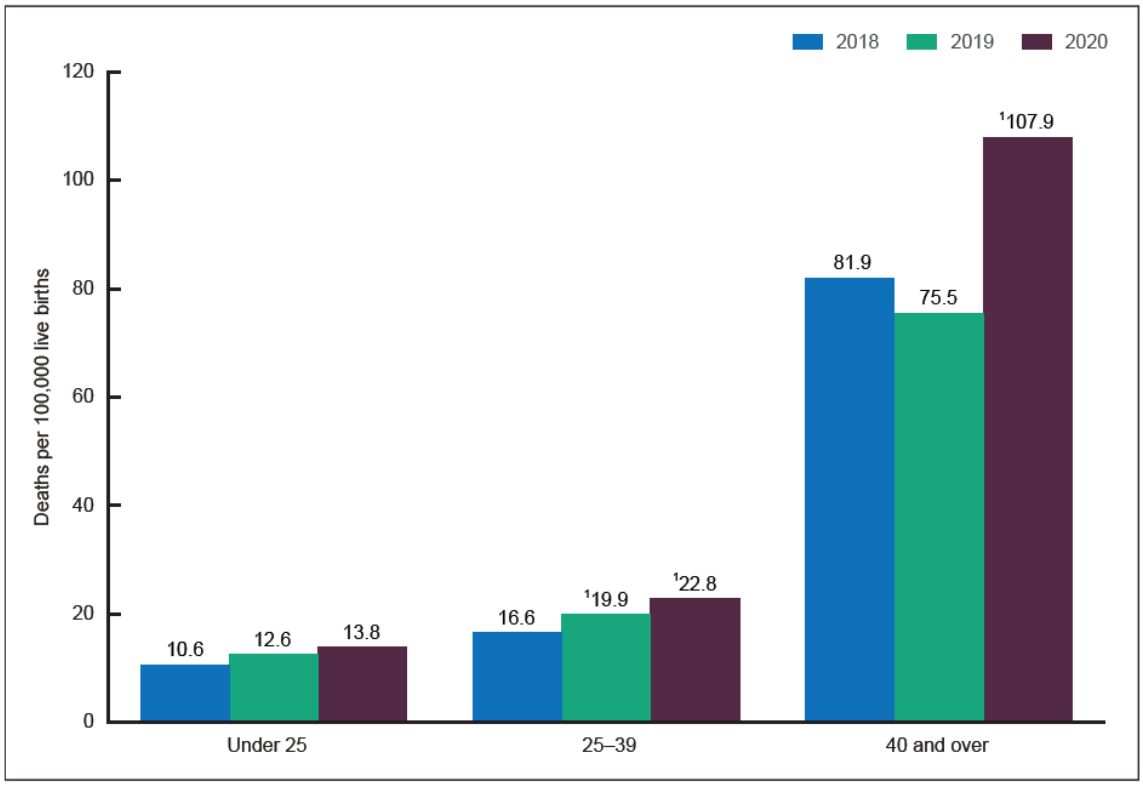
SOURCES: National Center for Health Statistics, National Vital Statistics System, Mortality and Natality.

Figure 1. Maternal mortality rates, by race and Hispanic origin: United States, 2018–2020



[1]Statistically significant increase in rate from previous year ($p < 0.05$).
NOTE: Race groups are single race.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

Figure 2. Maternal mortality rates, by age group: United States, 2018–2020



[1]Statistically significant increase in rate from previous year ($p < 0.05$).
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

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Maternal mortality, abortion access, and optimizing care in an increasingly restrictive United States: A review of the current climate

Nisha Verma[a], and Scott A. Shainker[b,c,*]

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ABSTRACT

The United States is facing a national crisis related to increasing rates of maternal morbidity and mortality. Over the past few years, significant focus has been turned to initiatives that aim to address maternal morbidity and mortality rates. In parallel, the United States has seen a significant increase in restrictive abortion access state laws. The link between abortion restrictions and worsening maternal outcomes has been proposed. This review article outlines the national crisis of maternal morbidity and mortality, the potential role of limiting abortion access in this crisis, and the significant racial, socioeconomic, and geographical disparities that exist.

Introduction

The death of a pregnant or postpartum woman is a uniquely tragic occurrence. Yet, in the United States (U.S.), the pregnancy related mortality (PRM) rate has steadily climbed from 1987 to 2016.[1] Slightly less than two pregnant or postpartum women die each day in the U.S., leading to approximately 700 maternal deaths per year.[2] No single cause has been identified to explain this continued rise; however, increasing rates of chronic co morbidities (specifically cardiovascular disease), increasing cesarean section rates, the aging maternal population, and racial and socioeconomic disparities in healthcare access are all speculated to play a role in this deadly epidemic.[3–9] Over recent years, significant focus has been turned to initiatives aimed at addressing maternal morbidity and mortality. Successful national efforts include the establishment of the National Partnership in Maternal Safety, expanding the focus and educational efforts around maternal care (i.e.: putting the "M" back in MFM), and the recent passing of H. R.1318 Preventing Maternal Deaths Act of 2018.[10–12] Along with the increasing rates of maternal mortality, there has been an alarming rise in severe maternal morbidity (SMM) and maternal near misses in the U.S.[11,13,14] In parallel with these disturbing trends, many new restrictions to abortion access have been passed over recent years.[15–17] This review outlines the national crisis of maternal morbidity and mortality, the alarming racial, socioeconomic, and geographical disparities that exist, and the potential role of limiting abortion access plays in this current crisis.

Dr. Shainker receives salary and research support from the Charles Koch Foundation.
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0146 0005/

JAMA Psychiatry | Original Investigation

Women's Mental Health and Well-being 5 Years After Receiving or Being Denied an Abortion
A Prospective, Longitudinal Cohort Study

M. Antonia Biggs, PhD; Ushma D. Upadhyay, PhD, MPH; Charles E. McCulloch, PhD; Diana G. Foster, PhD

Supplemental content

IMPORTANCE The idea that abortion leads to adverse psychological outcomes has been the basis for legislation mandating counseling before obtaining an abortion and other policies to restrict access to abortion.

OBJECTIVE To assess women's psychological well-being 5 years after receiving or being denied an abortion.

DESIGN, SETTING, AND PARTICIPANTS This study presents data from the Turnaway Study, a prospective longitudinal study with a quasi-experimental design. Women were recruited from January 1, 2008, to December 31, 2010, from 30 abortion facilities in 21 states throughout the United States, interviewed via telephone 1 week after seeking an abortion, and then interviewed semiannually for 5 years, totaling 11 interview waves. Interviews were completed January 31, 2016. We examined the psychological trajectories of women who received abortions just under the facility's gestational limit (near-limit group) and compared them with women who sought but were denied an abortion because they were just beyond the facility gestational limit (turnaway group, which includes the turnaway-birth and turnaway-no-birth groups). We used mixed effects linear and logistic regression analyses to assess whether psychological trajectories differed by study group.

MAIN OUTCOMES AND MEASURES We included 6 measures of mental health and well-being: 2 measures of depression and 2 measures of anxiety assessed using the Brief Symptom Inventory, as well as self-esteem, and life satisfaction.

RESULTS Of the 956 women (mean [SD] age, 24.9 [5.8] years) in the study, at 1 week after seeking an abortion, compared with the near-limit group, women denied an abortion reported more anxiety symptoms (turnaway-births, 0.57; 95% CI, 0.01 to 1.13; turnaway-no-births, 2.29; 95% CI, 1.39 to 3.18), lower self-esteem (turnaway-births, −0.33; 95% CI, −0.56 to −0.09; turnaway-no-births, −0.40; 95% CI, −0.78 to −0.02), lower life satisfaction (turnaway-births, −0.16; 95% CI, −0.38 to 0.06; turnaway-no-births, −0.41; 95% CI, −0.77 to −0.06), and similar levels of depression (turnaway-births, 0.13; 95% CI, −0.46 to 0.72; turnaway-no-births, 0.44; 95% CI, −0.50 to 1.39).

CONCLUSIONS AND RELEVANCE In this study, compared with having an abortion, being denied an abortion may be associated with greater risk of initially experiencing adverse psychological outcomes. Psychological well-being improved over time so that both groups of women eventually converged. These findings do not support policies that restrict women's access to abortion on the basis that abortion harms women's mental health.

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JAMA Psychiatry. 2017;74(2):169-178. doi:10.1001/jamapsychiatry.2016.3478
Published online December 14, 2016. Corrected on January 18, 2017.

From: (b)(6)/PPI
To: (b)(4)/TS-CI; (b)
Cc: (b)(6)/PPI
Subject: Information Request: NDA 020687
Date: Friday, July 22, 2022 2:37:14 PM
Importance: High

Hello (b)(4)/TS-CI; (b)(6)/PPI

Refer to your proposed modification to the single, shared system (SSS) REMS, the Mifepristone REMS Program, submitted on June 22, 2022. To support our review of your proposed modification, we request you provide responses to the following questions and comments. We also request you confirm receipt of our requests below and agree that you will respond by July 29, 2022. Submit your responses no later than July 29, 2022, as a REMS Correspondence.

General

1. Provide any feedback (e.g., pros and cons) obtained from stakeholders (e.g., patients, prescribers, retail pharmacies, specialty pharmacies and distributors) on any aspects of your proposed REMS modification. Specify which comments came from which stakeholders.
2. Provide schematics of all envisioned drug movement through the healthcare system from distributor to healthcare provider (HCP) to pharmacy and/or patient. The schematics should focus on how adherence to the REMS is ensured. If the model differs for a mail order pharmacy or a retail pharmacy, ensure you provide a separate schematic.

For the REMS element that addresses prescriber requirements

3. Your proposed modified REMS Document states (b)(4)/TS-CI [redacted].

(b)(4)/TS-CI [redacted]

e. Provide the criteria for decertification of a prescriber. Describe how:

Mifepristone SSS REMS

Sponsors' August 26, 2022 Response to FDA's Information Request

Dated July 22, 2022

General

1. *Provide any feedback (e.g., pros and cons) obtained from stakeholders (e.g., patients, prescribers, retail pharmacies, specialty pharmacies and distributors) on any aspects of your proposed REMS modification. Specify which comments came from which stakeholders.*

Response: Danco Laboratories, LLC ("Danco") and GenBioPro, Inc. ("GenBioPro") (together, the "Sponsors") jointly and independently have long engaged with multiple stakeholders, including: experts and providers from a broad spectrum of health care settings; mail, retail and other pharmacies, and; distributors. This engagement includes historical work with stakeholders since the initial mifepristone approval in 2000, work during the period since the lifting of the in-person dispensing requirement under the current enforcement discretion waiver and the prior court order and since the December 16, 2021 FDA letter regarding the REMS Modification ("REMS Modification").

The Sponsors have developed a deep understanding of the women's healthcare community, the needs, and burdens on patients, healthcare providers ("HCPs"), pharmacies and related stakeholders, which has informed the Sponsors at every turn including the proposed REMS Modification submitted on June 22, 2022.

Protection of patient and HCP privacy and confidentiality coupled with the need to provide the broadest access to the medical abortion by removing barriers to efficient delivery of care that are not needed to assure safe use have always been critical considerations in the availability of the product – even more so today. These considerations guide every decision, including the development and implementation of the risk mitigation efforts, starting with the Subpart H restrictions, through to the shared REMS. We now have over 20 years of experience with mifepristone, resulting in a significant body of data substantiating the safe and appropriate use of this product while continuing to protect privacy and access for patients and HCPs.

These critical considerations and understanding of stakeholder concerns were forefront in the development of the proposed REMS Modification that the Sponsors recently submitted and informed the responses to this Information Request.

The Sponsors have not shared the specific content of the proposed REMS Modification with any stakeholder, although high level discussions of broad

concepts for approaches were held in June with provider organizations, mail order pharmacies, pharmacy chains, reproductive rights attorneys, reproductive rights advocates, medical organizations, distributors and others.

Uniformly, all groups advocated that any changes to the REMS must lessen – and not increase – the current burdens on HCPs and patients to ultimately increase patient access to mifepristone, while maintaining privacy protections for HCPs, patients, pharmacies, and other important stakeholders. They also emphasized that approaches that might cause new risks, such as registries of certified HCPs that are unavoidably at risk of compromise, could cause existing certified HCPs to withdraw from offering mifepristone thus reducing patient access.

Most advocates were highly supportive of expansion to all types of pharmacies without any restrictions. The mail order pharmacies who are providing services currently under the REMS enforcement discretion wish to continue providing service under the new REMS. Additionally, some retail and other types of pharmacies have initiated requests to become certified and have requested us to ensure that workable systems are implemented and provide a sufficient level of confidentiality to providers. Some providers raised questions about availability through retail pharmacies citing the history with emergency contraception and that there are retail pharmacies that might not stock the drug given the low dispensing frequency and pharmacists on staff who might object to filling a prescription as conscientious objectors, though none believed that this is a reason to restrict access by pharmacy type. All groups strongly supported mail order pharmacy ("MOP") dispensing and believe that mail-order and local pharmacies anticipating reasonable dispensing volumes would be the first to quickly integrate mifepristone into their current operations. The proposed REMS Modification builds on that experience, and is designed to protect HCP and patient confidentiality, maximize access and operational efficiency while providing the same level of assurance of safe use as the current system.

Further, most stakeholders – particularly HCPs – continue to request the removal of both the Prescriber Agreement and Patient Agreement. to reduce the burden on them and their patients. They also expressed concern that in the current environment the requirement in the Patient Agreement for the patient to bring the Medication Guide to an "emergency room or a healthcare provider who did not give [me] mifepristone" places the patient at risk of being stigmatized, or

rejected for treatment or even being prosecuted in some states, and therefore should be removed.

Specifically, all stakeholders supported the following key elements of the proposed REMS Modification:

a. Removing the in-person dispensing requirement;

b. Removing all ambiguity that the REMS allows and directs (b)(4)/TS-CI a certified HCP and undertaken by in-person or telemedicine methods as determined appropriate in the clinical judgment of those healthcare providers;

c. (b)(4)/TS-CI ;

d. Removing purchasing account and shipping location information from the Prescriber Agreement Form; and

e. (b)(4)/TS-CI .

These uniform recommendations are reflected in the proposed REMS Modification and supported by the long history of safe and effective use of mifepristone.[1]

2. *Provide schematics of all envisioned drug movement through the healthcare system from distributor to healthcare provider (HCP) to pharmacy and/or patient. The schematics should focus on how adherence to the REMS is ensured. If the model differs for a mail order pharmacy or a retail pharmacy, ensure you provide a separate schematic.*

Response: The below diagram provides the requested schematic of drug movement and how adherence to the REMS is ensured. The proposal does not contemplate any differences based on pharmacy model.

[1] *See* FDA Adverse Event Reporting System ("FAERS") Reports for Mifepristone, Mifepristone REMS Assessment Report, dated April 9, 2020, *and* FDA Response to American Association of Pro-Life Obstetricians and Gynecologists and American College of Pediatricians, Docket No. FDA-2019-P-1534 at 20, 25-36 (Dec. 16, 2021) ("FDA Response to AAPLOG").

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

(b)(6)/PPI

Integrated (b)(6)/PPI **Memorandum**

Date: December 22, 2022

Reviewers: (b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

Product Name: Mifepristone 200 mg

Subject: All Adverse Events

Application Type/Number: NDA 020687; ANDA 091178

Applicants: Danco Laboratories, LLC; GenBioPro, Inc.

(b)(6)/PPI **#:** 2022-2987

2.3 LITERATURE SEARCH

We searched the medical literature with the strategy described in **Table 2**.

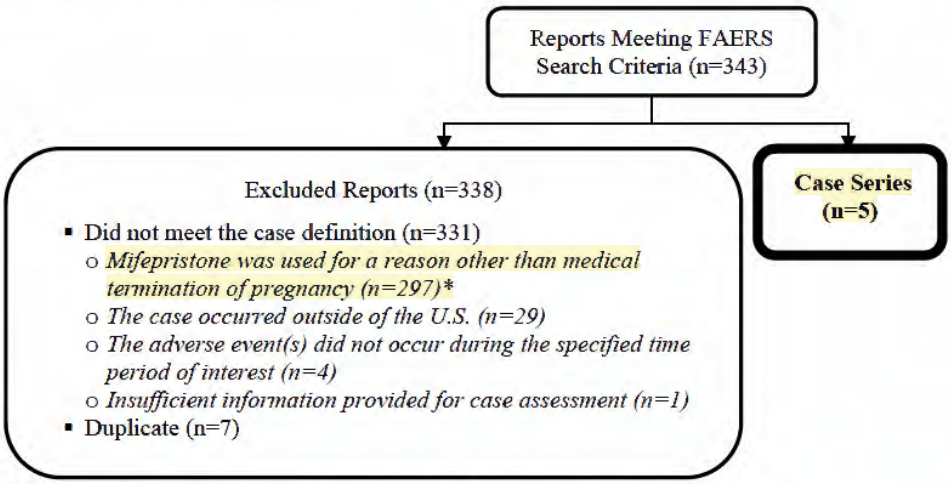
Table 2. Literature Search Strategy	
Date of search	December 4, 2022
Databases	Embase and PubMed
Search terms	Embase: ('mifepristone'/exp OR mifepristone) AND (2021:py OR 2022:py) AND 'case report'/de PubMed: (("mifepristone"[MeSH Terms] OR "mifepristone"[All Fields] OR "mifepriston"[All Fields]) AND ("case reports"[Publication Type] OR "case report"[All Fields])) AND (2021:2022/12/3[pdat])
Years included in search	2021 and 2022

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 343 reports. After applying the case definition in **Section 2.1** and accounting for duplicate reports, five cases were identified in which an adverse event reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy in the U.S. (see **Figure 1**).

Figure 1. FAERS Case Selection



* 295 reports documented the use of mifepristone for Cushing's syndrome (or related conditions) or specified the use of Korlym® and 2 reports documented the use of mifepristone for the management of early pregnancy loss.

We summarized the pertinent information from all five cases below. **Appendix B** contains a line listing of these five cases.

TTT # 2022-2468
NDA 020687
ANDA 091178
Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022

The following information is from United States (U.S.) post-marketing reports received by FDA of adverse events that occurred among patients who had taken mifepristone for medical termination of pregnancy. Because FDA has eliminated duplicate reports, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details, the numbers provided here may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. These events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use, and other possible medical or surgical treatments and conditions. The estimated number of women who have used mifepristone in the U.S. for medical termination of pregnancy through the end of June 2022 is approximately 5.6 million women.

For informational purposes, fatal foreign cases that were reported after U.S. approval of mifepristone for medical termination of pregnancy are also included in a footnote in Table 1.

Table 1. Cumulative Post-Marketing Fatal and Ectopic Pregnancy Reports in U.S. Women Who Used Mifepristone for Medical Termination of Pregnancy

Date range of cumulative reports	09/28/00[†] - 06/30/22
Died [‡]	28
*Ectopic pregnancies [||]	97

[†] U.S. approval date

[‡] The fatal cases are included regardless of causal attribution to mifepristone. Deaths were associated with sepsis in nine of the 28 reported fatalities (eight cases tested positive for *Clostridium sordellii*, and one case tested positive for *Clostridium perfringens*). Eight of the nine fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Eighteen of the 19 remaining U.S. deaths involved two cases of homicide, two cases of combined drug intoxication/overdose, two cases of ruptured ectopic pregnancy, two cases of drug intoxication, and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; delayed onset toxic shock-like syndrome; hemorrhage; bilateral pulmonary thromboemboli; unintentional overdose resulting in liver failure; probable anaphylactic medication reaction; and a case of natural death due to severe pulmonary emphysema. In the nineteenth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. There were 13 additional reported deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure;" thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); sepsis (*Enterococcus faecalis* and *Escherichia coli* were identified in blood culture); asthma attack with cardiac arrest; thromboembolism; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium septicum* sepsis (from a published literature report).

* The majority of these women are included in the hospitalized category in Table 2.

[||] Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

[redacted] and [redacted]

Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
[redacted] #	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.[a] The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg 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 by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

[a] The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement" for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency's REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Per the Agency's December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.[c] Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.[1-5] On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.[6-7] The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program 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 (under ETASU A).
b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[8]

[c] Mifepristone is also approved in approximately 80 other countries. https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.[9]
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.[10]
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system[d] REMS could be implemented using the existing email and facsimile based system, (b) (4) , as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4) , as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4) .
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

[d] "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form, Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6) ; hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone 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 by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.[11]

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.[11] After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the "in-person dispensing requirement"), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient's medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber's signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

***Reviewer Comment**: We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

***Reviewer Comment:** We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

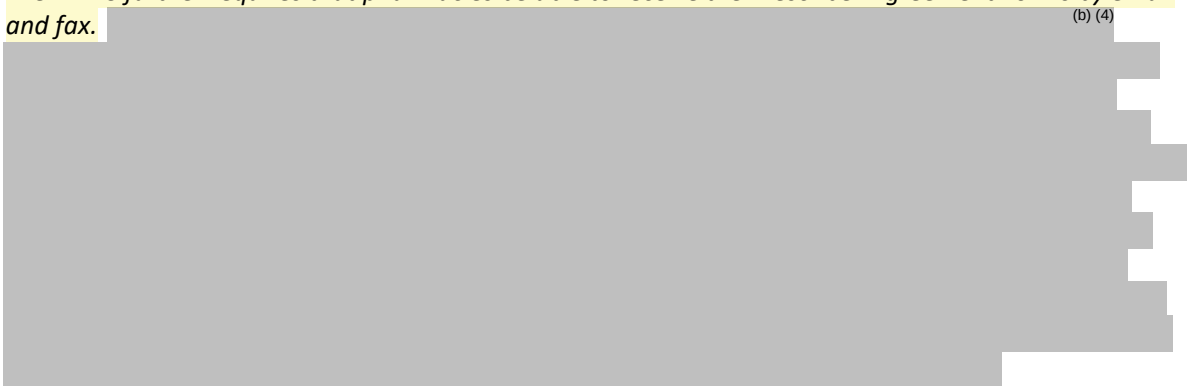
The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.[e] *Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

[e] See e.g., *2020 Violence and Disruption Statistics,* National Abortion Federation (Dec. 16, 2021), https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/.

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax. (b) (4)



The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,[13] while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

***Reviewer's Comment**: We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

***Reviewer's Comment**: We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program 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.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

c. Informing patients about the risk of serious complications associated with mifepristone.
    - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
        - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
        - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
        - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
        - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment*: We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4) . The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form.* Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.[13, 14]

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.

2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.

3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.

4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.

5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.

6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.

7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.

8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2022; 107:36-41. https://doi.org/10.1016/j.contraception.2021.09.008. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone 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 by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
         2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
   b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
      i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
      ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms "sign" and "signature" include electronic signatures.

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified

   a. To become specially certified to dispense mifepristone, pharmacies must:

      i. Be able to receive *Prescriber Agreement Forms* by email and fax.

      ii. Be able to ship mifepristone using a shipping service that provides tracking information.

      iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.

      iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:

         1) Review the Prescribing Information for mifepristone.

         2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:

            a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.

            b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.

            c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.

            d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.

            e) Track and verify receipt of each shipment of mifepristone.

            f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.

            g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.

            h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.

            i) Maintain records of *Prescriber Agreement Forms*.

            j) Maintain records of dispensing and shipping.

            k) Maintain records of all processes and procedures including compliance with those processes and procedures.

            l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.

            m) Train all relevant staff on the Mifepristone REMS Program requirements.

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

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*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com
2023 SUPP 001139

Reference ID: 5103819

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take mifepristone on Day 1.
   b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

2023 SUPP 001143

Reference ID: 5103819

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
  - Track and verify receipt of each shipment of Mifeprex.
  - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

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P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

2023 SUPP 001144

Reference ID: 5103819

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

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1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

2023 SUPP 001145

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
  - Track and verify receipt of each shipment of mifepristone.
  - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies
      i. Number of certified pharmacies
      ii. Number and percentage of newly certified pharmacies
      iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
   c. Wholesalers/Distributors
      i. Number of authorized wholesalers/distributors
      ii. Number and percentage of newly authorized wholesalers/distributors
      iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
   a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
   b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
   a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
      i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
      v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:

i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)

ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):

1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance
4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non-compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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NATIONAL ABORTION FEDERATION

2020 VIOLENCE AND DISRUPTION STATISTICS

Despite a global pandemic, abortion providers continued to experience an escalation in targeted violence and disruption in 2020. Abortion providers reported an increase in vandalism, assault and battery, death threats/threats of harm, stalking, and hoax devices/suspicious packages from 2019.

2020 VIOLENCE AND DISRUPTION STATITICS

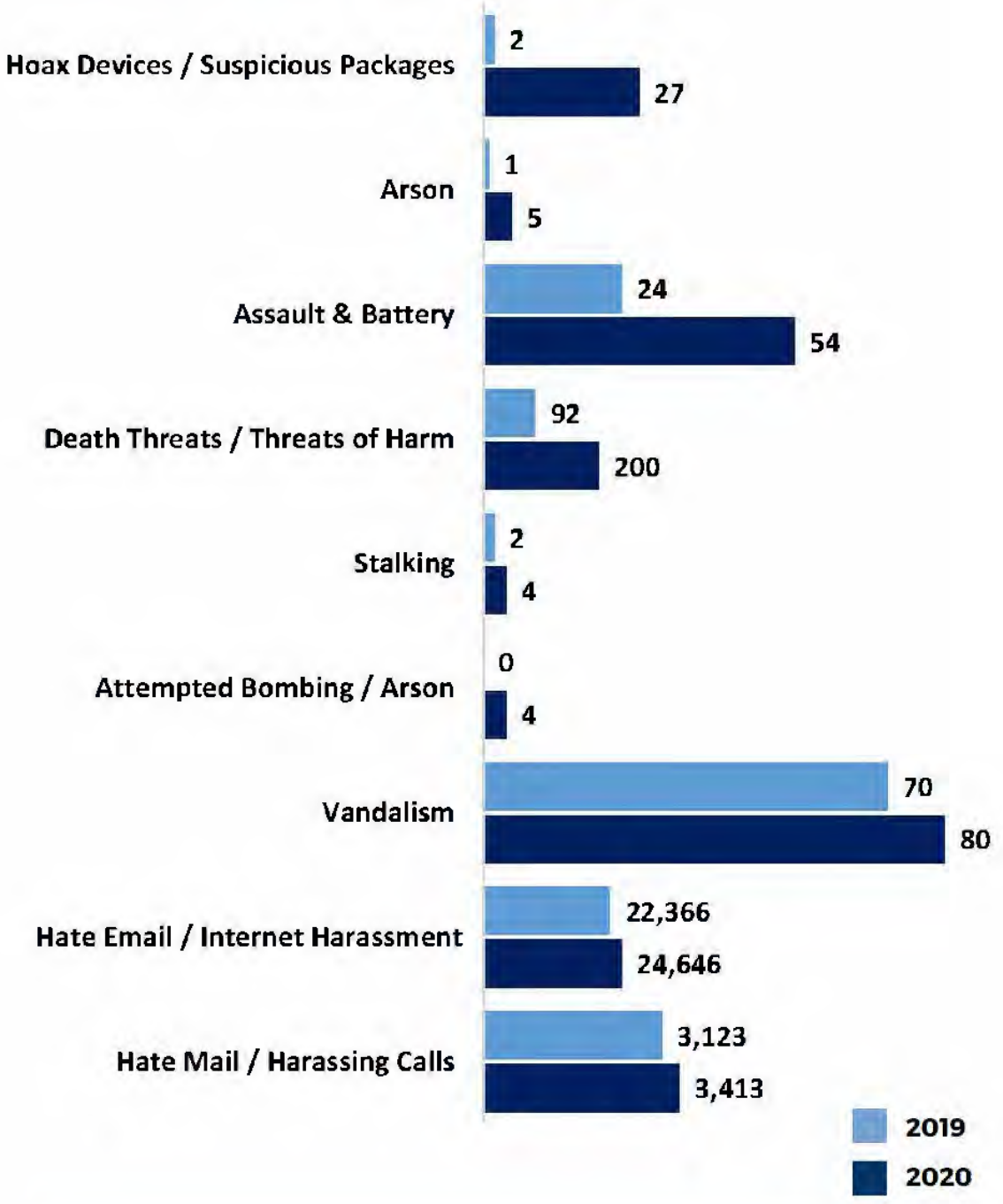
Throughout 2020, anti-abortion individuals and groups exploited the COVID-19 pandemic, racial justice uprisings, and 2020 elections as opportunities to harass abortion providers.

Anti-abortion protesters congregated outside abortion clinics despite stay-at-home orders and public health guidance to avoid group gatherings, and we observed an alarming trend of armed, white supremacist individuals meeting outside NAF member facilities and protesters co-opting the language of the movement for Black lives in their attempts to intimidate providers and patients.

Emboldened by the passage and enforcement of abortion restrictions in several states, anti-abortion individuals and groups continued to harass abortion providers this year. A January 2020 unclassified report from the FBI outlined an ongoing increase in anti-abortion threats, disruption, and violence, stating, "The FBI assesses the increase in abortion-related violent extremist threats and criminal activity, including violations of the Freedom of Access to Clinic Entrances (FACE) Act, against targets including reproductive healthcare facilities (RHCFs) likely is driven in part by the recent rise in state legislative activities related to abortion services and access."

Abortion providers reported an increase in vandalism, assault and battery, death threats/threats of harm, stalking, and hoax devices/suspicious packages from 2019.

2020 INCREASES



Wyoming authorities search for a suspect believed to have set an abortion clinic on fire

By Amanda Musa, CNN

Published 12:08 AM EDT, Sat June 11, 2022

Casper Police Department

Surveillance video shows the suspect believed to have set fire to a Wyoming abortion clinic, police say.

(CNN) — Local and federal authorities are searching for a suspect who they believe intentionally set fire to an abortion clinic set to open in Casper, Wyoming, later this month.

The suspected arson took place in the early morning hours of May 25, according to a news release from the Casper Police Department.

Surveillance video from inside the Wellspring Health Access clinic shows the suspect, whose face is covered with a surgical mask most of the time, carrying a red gas canister. Police released the footage earlier this week.

When police responded to the business shortly after the suspect was caught on video, they found a broken window and saw a fire, according to the police news release.

Authorities believe the suspect is a white female and acted alone, according to the news release.

The Denver field division of the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) is offering a $5,000 reward to anyone who provides information leading to the suspect's arrest, police said. Authorities are also working with the FBI, police said.

The clinic was set to open in mid-June, but the open date has now been pushed back for months.

RELATED ARTICLE
13 states have passed so-called 'trigger laws,' bans designed to go into effect if Roe v. Wade is overturned

"We're still working with our contractors and insurance adjuster to determine the full extent and cost of the damages. At this point, we're anticipating that the clinic opening will be delayed by around six months," Julie Burkhart, president and founder of the Wellspring Health Access told CNN in a statement on Friday.

"Despite these setbacks, we are undeterred in our mission to give the people of Casper access to comprehensive reproductive health care, including abortion care," Burkhart added.

The clinic in Casper is "strategically located so that people in areas of low access states such as western Nebraska, western South Dakota, and the southeastern corner of Montana will be able to more easily access health care services," according to the clinic's website.

Casper, a city of nearly 60,000 residents, is in the central part of the state.

When it does open, the clinic is expected to become the only clinic offering both medication and surgical abortions in the state of Wyoming, according to health

medication and surgical abortions in the state of Wyoming, according to Wellspring Health Access.

Currently, the sole abortion provider in the state, Women's Health and Family Care in Jackson, Wyoming, only provides medication abortions for pregnancies under 10 weeks, the clinic said.

Wyoming is among a handful of other states that have passed "trigger laws," which are bans designed to go into effect if Roe v. Wade is overturned. The 1973 court decision affirmed the right to receive an abortion under the 14th Amendment, ruling abortions were constitutionally protected up until about 23 weeks when a fetus could be able to live outside the womb.

Signed into law earlier this year, Wyoming's bill added a provision which would make it illegal to perform an abortion if Roe is overturned, with extremely limited exceptions for cases of sexual assault, incest, or the risk of death or severe injury to the person giving birth.

CNN's Hannah Sarisohn, Elizabeth Wolfe and Paradise Afshar contributed to this report.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3).
Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

----------INDICATIONS AND USAGE----------
MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------
- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------
- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------
- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program *[see Warnings and Precautions (5.3)]*.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration
    One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1

    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)].*

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIFEPRISTONE TABLETS, 200 mg safely and effectively. See full prescribing information for Mifepristone tablets, 200 mg.

MIFEPRISTONE tablets, 200 mg for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following Mifepristone tablets, 200 mg use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

Mifepristone tablets, 200 mg is only available through a restricted program called the mifepristone REMS Program (5.3).

Before prescribing Mifepristone tablets, 200 mg, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

----------INDICATIONS AND USAGE----------

Mifepristone tablets, 200 mg is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------

- 200 mg Mifepristone on Day 1, followed 24-48 hours after Mifepristone dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GenBioPro, Inc. at 1-855-643-3463 or medical@genbiopro.com or MIFEINFO.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following Mifepristione tablets, 200 mg use. No causal relationship between the use of Mifepristone tablets, 200 mg and misoprostol and these events has been established.

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, Mifepristone tablets, 200 mg is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program *[see Warnings and Precautions (5.3)]*.

Before prescribing mifepristone, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

Mifepristone tablets, 200 mg is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

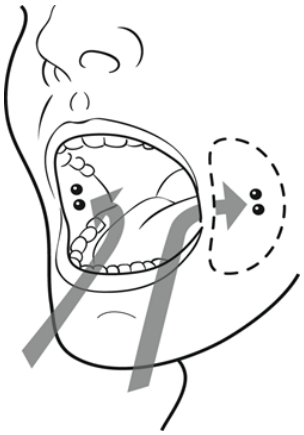
Remove any intrauterine device (“IUD”) before treatment with Mifepristone tablets, 200 mg begins [*see Contraindications (4)*].

The dosing regimen for Mifepristone tablets, 200 mg and misoprostol is:

- Mifepristone 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* Mifepristone 200 mg Administration
    One 200 mg tablet of Mifepristone is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between Mifepristone and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1

    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking Mifepristone tablets, 200 mg must take misoprostol within 24 to 48 hours after taking Mifepristone. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)]*.

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take mifepristone on Day 1.
   b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

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Reference ID: 5103833