ATTACHMENT ONE

LIFE AND FAMILY INITIATIVE

The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event

ETHICS AND PUBLIC POLICY CENTER
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Summary

- This largest-known study of the abortion pill is based on analysis of data from an all-payer insurance claims database that includes 865,727 prescribed mifepristone abortions from 2017 to 2023.
- 10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious adverse event within 45 days following a mifepristone abortion.
- The real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label.
- The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects.
- The FDA should further investigate the harm mifepristone causes to women and, based on objective safety criteria, reconsider its approval altogether.

Danco Laboratories markets Mifeprex as "the safe and effective abortion pill," but our research shows that mifepristone abortion, as currently practiced in the U.S., is not safe and effective.[1] The manufacturer and the FDA rely on the results of 10 clinical trials with a total of 30,966 participants, less than 0.5 percent of whom reportedly experienced serious adverse reactions. In contrast, we analyzed real-world insurance claims data for 865,727 prescribed mifepristone abortions, broadly representative of women who obtain mifepristone abortions in the U.S. today, and we find a serious adverse event rate of 10.93 percent—at least 22 times as high as the summary figure reported on the drug label. In light of this research, we urge the FDA to reinstate earlier, stronger patient safety protocols and reconsider its approval of mifepristone altogether. Women deserve better than the abortion pill.

Our Key Findings

10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious or life-threatening adverse event within 45 days following a mifepristone abortion, far greater than the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label. *Figure 1, next page.*

[1] Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprix (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)

Figure 1

Serious Adverse Events by Category

	Number with adverse events	Serious adverse event rate
Sepsis	824	0.10%
Infection	11,707	1.34%
Transfusion	1,257	0.15%
Hemorrhage	28,658	3.31%
Hospitalization (related to the abortion)	5,699	0.66%
ER visit (related to the abortion)	40,960	4.73%
Ectopic pregnancy	3,062	0.35%
Other life-threatening adverse events (cardiac, pulmonary, thrombosis, anaphylaxis, surgery)	1,956	0.22%
Repeated (surgical) abortion	24,563	2.84%
Other abortion-specific complications	49,169	5.68%
Overall	94,605	10.93%

Note: The overall serious adverse event rate of 10.93% is adjusted for the fact that some women suffer from adverse events in multiple categories.

Simply stated, mifepristone, as used in real-world conditions, is not "safe and effective."

Our real-world post-market observational study of mifepristone is, to our knowledge, the most comprehensive study of chemical abortion safety ever conducted in the U.S.:

- We identify and include 865,727 prescribed mifepristone abortions, 28 times as many as were included in all FDA-cited clinical trials combined.
- Our dataset is more recent, no earlier than 2017, while the FDA approval of mifepristone relies entirely on data from more than a decade ago.
- The women in our dataset are broadly representative of the women who obtain mifepristone abortions in the U.S.; they are not a prescreened group of generally healthy women recruited into various clinical trials conducted at different times around the world.
- The women in our dataset receive (or fail to receive) pre- and post-abortion healthcare of the real-world quality that prevails in the U.S. today, not the carefully controlled regimen of care that ordinarily prevails in a clinical trial.

Policy Implications

The FDA should reinstate the original patient safety protocols that were required when mifepristone was first approved. Doing so will likely reduce the harms to women and permit better monitoring to determine whether this drug should remain on the market:

- Prescribing mifepristone and misoprostol for the termination of pregnancy should require at least three in-person office visits by the patient—as originally required by the FDA.
- Mifepristone should be prescribed only by physicians—as originally required by the FDA—who have read and understood the prescribing information.
- Mifepristone should be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies—all of which was originally required by the FDA.
- Physicians must be able 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.
- Healthcare providers should be required once again to report to the FDA (and manufacturers of mifepristone) all serious adverse events resulting from the use of mifepristone.
- Mifepristone should only be prescribed to a woman who is confirmed by a physician to be in the first seven weeks of pregnancy—as originally required by the FDA.

Background on FDA Approval and Regulation of Mifepristone

Mifepristone was developed by the French pharmaceutical company Roussel Uclaf S.A. and brought to the United States at the urging of President Clinton and after Congressional pressure. The FDA approved it under a little-used approval process for "certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments."[2] Thus, to grant approval in this manner, the FDA had to consider an unwanted pregnancy a "serious or life-threatening illness" and find that mifepristone was more effective than surgical abortion in treating it. The FDA's decision cites minimal data: clinical trials with only 859 participants in the U.S. and 1,800 in France.[3]

The original FDA-approved drug label for Mifeprex (the brand name of mifepristone) from September 2000 indicated use of the drug for "the medical termination of intrauterine pregnancy through 49 days' pregnancy."[4] It required several modest safeguards for women's health:

> Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able 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.[5]

During the Obama and Biden administrations, the FDA chipped away at these initial safeguards, risking women's health in order to increase access to abortion. Under the current Risk Evaluation and Mitigation Strategy (REMS) in effect since 2023:

1. a mifepristone abortion now requires as a little as one telehealth visit with any approved healthcare provider (not necessarily a physician),
2. a woman may self-administer drugs obtained from a mail-order pharmacy, and
3. the prescriber need not report any adverse events unless he or she knows that a patient has died. *Figure 2.*

Figure 2

Weakening FDA Safeguards for Mifepristone

	2000 Clinton Initial Approval	2016 Obama REMS Changes	2023 Biden REMS Changes
Required number of in-person visits	3	1	0
Maximum gestational age (LMP)	7 weeks	10 weeks	10 weeks
Drugs prescribed only by physician	✓	✗	✗
Drugs dispensed only in office	✓	✓	✗
Drugs taken only in office	✓	✗	✗
Required in-office follow-up	✓	✗	✗
Required reporting of adverse events	✓	✗	✗

2 Alliance for Hippocratic Medicine v. FDA, Complaint, https://adflegal.org/wp-content/uploads/2022/11/Alliance-for-Hippocratic-Medicine-v-FDA-2022-11-18-Complaint.pdf
3 Mifeprex (mifepristone) drug label, September 2000, page 3, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf
4 Mifeprex (mifepristone) drug label, September 2000, page 6, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf
5 Mifeprex (mifepristone) drug label, September 2000, page 14, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf

The current FDA-approved drug label refers to the results of 10 clinical trials with a total of 30,966 participants, less than 0.5 percent of whom reportedly experienced serious adverse reactions.[6] But these figures are based entirely on data from trials taking place more than a decade ago.

The Increasing Market Share of Chemical Abortion

Increased access to chemical abortion has coincided with a rapid increase in its prevalence. Chemical abortions—the vast majority of which are performed using a combination of mifepristone and misoprostol—now account for roughly two-thirds of all abortions in the United States. *Figure 3.*

In fact, Danco Laboratories boasts that more than 5 million U.S. women have used its abortion pill since it was approved in 2000.[7] Thus, it has become increasingly important to understand the risks and harms to women from chemical abortion in general and from mifepristone in particular.

How We Identified Mifepristone Abortions

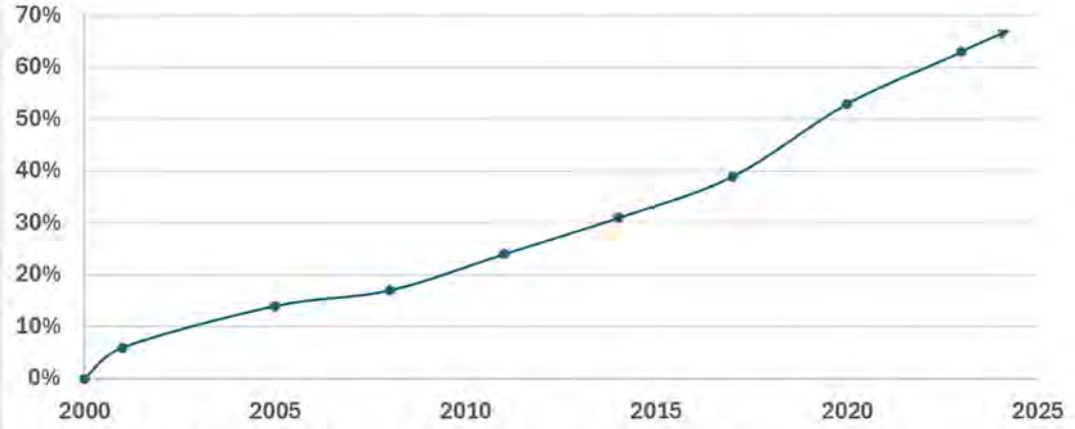
In our data, a mifepristone abortion was identified in one of three ways:

1. procedure code S0199: medically induced abortion by oral ingestion of medication including all associated services and supplies,
2. a prescription for mifepristone (with or without misoprostol within the next 3 days), or
3. a diagnosis code for elective termination or unwanted pregnancy, along with other billing coding consistent with manufacturer instructions for reimbursement for a mifepristone abortion for a given state and insurer combination.[8]

Following this method, we identified a total of 865,727 mifepristone abortions prescribed for a total of 692,873 women from 2017 to 2023. This includes 566,446 women, each of whom had one such abortion, and 126,427 women with multiple such abortions.

Figure 3

Chemical abortion has increased rapidly since approval in 2000 and now accounts for approximately two-thirds of all abortions.



Source: Guttmacher Abortion Provider Census and Monthly Abortion Provision Study, via https://www.guttmacher.org/2024/03/medication-abortion-accounted-63-all-us-abortions-2023-increase-53-2020

6 Page 7 of the drug label states, "Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2." Table 2 on page 8 indicates that some categories of serious adverse reactions were observed at higher rates in some trials, but this is never discussed in the text, leaving only the previous statement with which to interpret the table. See Mifeprex (mifepristone) drug label, January 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf

7 Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprex (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)

8 Danco Laboratories, "Mifeprex State Payer Policies," https://www.earlyoptionpill.com/how-do-i-get-mifeprex/state-payer-policies (accessed April 14, 2025)

How We Identified Serious Adverse Events

We followed the official FDA definition of "serious adverse event."[9] To do so, we identified relevant ICD-10 diagnosis codes and CPT/HCPCS procedure codes for adverse events from multiple sources:

- CDC Severe Maternal Morbidity (SMM) indicators,[10]
- CMS Diagnosis-Related Group (DRG) 770 and 769 codes,[11]
- FDA Adverse Events Reporting System (FAERS) reports (interpreted and translated into diagnosis and procedure codes by the doctors on our team),[12] and
- a small number of (mostly gynecological) codes suggested by our doctors.

These codes were then graded by a team of physicians using the the NIH Common Terminology Criteria for Adverse Events (CTCAE version 5), which categorizes adverse events by severity on a 5-point scale.[13] We included CTCAE Grade 3 (severe) and Grade 4 (life-threatening). We did not include Grade 1 (mild) or Grade 2 (moderate). (Grade 5 is death, which would count as a serious adverse event under the FDA definition but could not necessarily be observed in the insurance claims data. We hope to show the rate of death in a subsequent report.)

For reporting, we have grouped the relevant diagnosis and procedure codes as follows:

1. The mifepristone label divides serious adverse events into six categories identified in the clinical trials: sepsis, infection, transfusion, hemorrhage, hospitalization, and emergency room visit. Only those hospitalizations and emergency room visits with abortion-related diagnosis and procedure codes are included in our analysis.
2. FAERS received reports of various events that our doctors judge to be life-threatening and have grouped into broad categories: ectopic pregnancy, surgery, cardiac, pulmonary, thrombosis, and anaphylaxis.
3. Repeated (surgical) abortion procedures are considered serious adverse events.
4. Other abortion complications include codes specifically related to an abortion or miscarriage, as well as life-threatening mental health diagnoses, etc.

We consider only serious adverse events that occurred within 45 days following the abortion. This is conservative, as some adverse events may present later (and studies relied on by the FDA used a timeframe as long as 72 days). Additionally, the likelihood of a subsequent pregnancy within this timeframe is negligible, which ensures that adverse events are related to the abortion rather than to a subsequent pregnancy.

Our Data

Our team has purchased access to a commercially available all-payer health insurance claims database including de-identified data for all U.S. patients during the years 2017 to 2023. It includes information on hospital and office visits, diagnoses, procedures, and prescriptions processed through private health insurance, Medicaid, Medicare, TRICARE, and the Department of Veterans Affairs (VA). The data excludes transactions for which the insurer is also the provider (as is the case with some HMOs and much VA care), as well as cash pay transactions (which are disproportionately common for abortion). This dataset provides longitudinal tracking of medical diagnoses, procedures, and prescriptions for each patient and is widely used in academic and regulatory research.

9 FDA, "What is a Serious Adverse Event?," https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event
10 CDC, "Identifying Severe Maternal Morbidity (SMM)," https://www.cdc.gov/maternal-infant-health/php/severe-maternal-morbidity/icd.html
11 CMS, "ICD-10-CM/PCS MS-DRG v37.0 Definitions Manual," https://www.cms.gov/icd10m/version37-fullcode-cms/fullcode_cms/P0287.html
12 FDA, "FDA Adverse Events Reporting System (FAERS) Public Dashboard," https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f-7f1c25ee/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis
13 NIH, "Common Terminology Criteria for Adverse Events (CTCAE)," https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Our Research Project Team

Our research project was conducted and validated by a team of data scientists, analysts, and engineers, with assistance from our clinical team of board-certified obstetricians and gynecologists. Members have a history of academic research and peer-reviewed publication.

Conclusion

Our research shows unequivocally that mifepristone abortion, as currently practiced in the U.S., is considerably more dangerous to women than is represented on the FDA-approved drug label. The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects. The FDA should further investigate the harm this drug causes to women and, based on objective safety criteria, reconsider its approval altogether. Women deserve better than the abortion pill.

This paper is the first in a series investigating women's health and abortion using real-world data.

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ATTACHMENT TWO

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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*

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosing Regimen
2.2 Patient Management Following Misoprostol Administration
2.3 Post-treatment Assessment: Day 7 to 14
2.4 Contact for Consultation
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infections and Sepsis
5.2 Uterine Bleeding
5.3 Mifepristone REMS Program
5.4 Ectopic Pregnancy
5.5 Rhesus Immunization
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)
7.2 Drugs that May Increase Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)
7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

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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:

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- 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.

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2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute adrenal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
  - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
  - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

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- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX *[see Boxed Warning]*. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. 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. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion *[see Boxed Warning]*.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

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5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the Mifepristone REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the Mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)]*. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

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About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

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Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

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regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

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misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

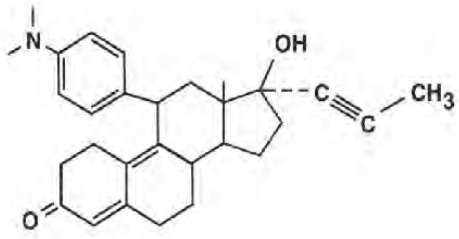
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

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of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

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Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

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Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	**%**	**Number of Evaluable Studies**	**N**	**%**	**Number of Evaluable Studies**	**N**	**%**	**Number of Evaluable Studies**	**N**	**%**	**Number of Evaluable Studies**
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

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17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [*see Warnings and Precautions (5.2)*].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [*see Warnings and Precautions (5.1, 5.2)*].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [*see Warnings and Precautions (5.3)*]. Under the Mifepristone REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- 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, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

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Manufactured for:
Danco Laboratories, LLC
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www.earlyoptionpill.com

03/2023

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MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

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What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

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How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 03/2023

ATTACHMENT THREE

Morbidity and Mortality Weekly Report (*MMWR*)

Abortion Surveillance — United States, 2022

Surveillance Summaries / November 28, 2024 / 73(7);1–28

Abstract

Problem/Condition: CDC conducts abortion surveillance to document the number and characteristics of women obtaining legal induced abortions and the number of abortion-related deaths in the United States.

Period Covered: 2022.

Description of System: Each year, CDC requests abortion data from the central health agencies for the 50 states, the District of Columbia, and New York City. For 2022, a total of 48 reporting areas voluntarily provided aggregate abortion data to CDC. Of these, 47 reporting areas provided data each year during 2013–2022. Census and natality data were used to calculate abortion rates (number of abortions per 1,000 women aged 15–44 years) and ratios (number of abortions per 1,000 live births), respectively. Abortion-related deaths from 2021 were assessed as part of CDC's Pregnancy Mortality Surveillance System (PMSS).

Results: For 2022, a total of 613,383 abortions were reported to CDC from 48 reporting areas. Among 47 reporting areas with data each year during 2013–2022, in 2022, a total of 609,360 abortions were reported, the abortion rate was 11.2 abortions per 1,000 women aged 15–44 years, and the abortion ratio was 199 abortions per 1,000 live births. From 2021 to 2022, the total number of abortions decreased 2% (from 622,108 total abortions), the abortion rate decreased 3% (from 11.6 abortions per 1,000 women aged 15–44 years), and the abortion ratio decreased 2% (from 204 abortions per 1,000 live births). From 2013 to 2022, the total number of reported abortions decreased 5% (from 640,154), the abortion rate decreased 10% (from 12.4 abortions per 1,000 women aged 15–44 years), and the abortion ratio increased 1% (from 198 abortions per 1,000 live births).

In 2022, women in their 20s accounted for more than half of abortions (56.5%). Women aged 20–24 and 25–29 years accounted for the highest percentages of abortions (28.3% and 28.2%, respectively) and had the highest abortion rates (18.1 and 18.7 abortions per 1,000 women aged 20–24 and 25–29 years, respectively). By contrast, adolescents aged <15 years and women aged ≥40 years accounted for the lowest percentages of abortions (0.2% and 3.6%, respectively) and had the lowest abortion rates (0.4 and 2.5 abortions per 1,000 women aged <15 and ≥40 years, respectively). However, abortion ratios were highest among adolescents (aged ≤19 years) and lowest among women aged 30–39 years. From 2021 to 2022, abortion rates decreased among women aged ≥20 years and did not change among adolescents (aged ≤19 years). Abortion rates decreased from 2013 to 2022 among all age groups, except women aged 30–34 years for whom it increased. The decrease in the abortion rate from 2013 to 2022 was highest among adolescents compared with other age groups. From 2021 to 2022, abortion ratios increased for adolescents and decreased among women aged ≥20 years. From 2013 to 2022, abortion ratios increased among adolescents and women aged 20–34 years and decreased among women aged ≥35 years. In 2022, the majority (78.6%) of abortions were performed at ≤9 weeks' gestation, and nearly all (92.8%) were performed at ≤13 weeks' gestation. During 2013–2022, the percentage of abortions performed at >13 weeks' gestation remained low (≤8.7%). In 2022, the highest

percentage of abortions were performed by early medication abortion at ≤9 weeks' gestation (53.3%), followed by surgical abortion at ≤13 weeks' gestation (35.5%), surgical abortion at >13 weeks' gestation (6.9%), and medication abortion at >9 weeks' gestation (4.3%); all other methods were uncommon (<0.1%). Among those that were eligible (≤9 weeks' gestation), 70.2% of abortions were early medication abortions. In 2021, the most recent year for which PMSS data were reviewed for pregnancy-related deaths, five women died as a result of complications from legal induced abortions.

Interpretation: Among the 47 areas that reported data continuously during 2013–2022, overall decreases were observed over this time in the number and rate of reported abortions and an increase was observed in the abortion ratio; in addition, from 2021 to 2022, decreases of 2%–3% were observed across all measures.

Public Health Action: Abortion surveillance can be used to help evaluate programs aimed at promoting equitable access to patient-centered quality contraceptive services in the United States to reduce unintended pregnancies.

Related Materials

Article PDF

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View suggested citation

Top

Introduction

This report summarizes data on legal induced abortions for 2022 that were provided voluntarily to CDC by the central health agencies of 48 reporting areas (46 states, the District of Columbia, and New York City, excluding California, Maryland, New Hampshire, and New Jersey) and comparisons over time for the 47 reporting areas that reported each year during 2013–2022 (46 states and New York City). This report also summarizes abortion-related deaths reported voluntarily to CDC for 2021 as part of the Pregnancy Mortality Surveillance System (PMSS). Since 1969, CDC has conducted abortion surveillance to document the number and characteristics of women obtaining legal induced abortions in the United States. After nationwide legalization of abortion in 1973, the total number, rate (number of abortions per 1,000 women aged 15–44 years), and ratio (number of abortions per 1,000 live births) of reported abortions increased rapidly, reaching the highest levels in the 1980s, before decreasing at a slow yet steady pace (*1,2*). During 2006–2008, a break occurred in the previously sustained pattern of decrease (*3,4*), although this break was followed in subsequent years by even greater decreases (*5,6*). However, from 2018 to 2019, increases of 1%–3% were observed across all measures (*7*). From 2019 to 2020, decreases were observed in the number and rate of reported abortions; however, a 2% increase was observed in the abortion ratio (*8*). From 2020 to 2021, increases of 4%–5% were observed across all measures (*9*). Abortion incidence and practices have varied over the years and continue to vary across subpopulations (*10–15*), highlighting the utility of continued surveillance.

Top

Methods

Description of the Surveillance System

Each year, CDC requests aggregate data from the central health agencies of the 50 states, the District of Columbia, and New York City to document the number and characteristics of women obtaining legal induced abortions in the United States. Not all persons who obtain abortions identify as women; the term "women" has been maintained in this report to be consistent with the collection and reporting of denominator data used to calculate abortion rates and ratios. This report contains data for 2022 voluntarily reported to CDC as of July 15, 2024. For the purpose of surveillance, legal induced abortion is defined as an intervention performed within the limits of state and jurisdiction law by a licensed clinician (e.g., a physician, nurse-midwife, nurse practitioner, or physician assistant) intended to terminate a suspected or known intrauterine

pregnancy and that does not result in a live birth. This definition excludes management of intrauterine fetal death, early pregnancy failure or loss, ectopic pregnancy, or retained products of conception. All abortions in this report are considered to be legally induced unless stated otherwise.

In most states and jurisdictions, collection of abortion data is facilitated by a legal requirement for hospitals, facilities, or physicians to report abortions to a central health agency (*16*); however, reporting is not complete in all areas, including in certain areas with reporting requirements (*17*). The reporting of abortion data to CDC is voluntary, and many reporting areas have developed their own data collection forms and might not collect or provide all the information requested by CDC. As a result, the level of detail reported to CDC might vary from year to year and by reporting area. To encourage uniform collection of data, the National Association for Public Health Statistics and Information Systems (NAPHSIS), with technical assistance from CDC, developed technical guidance for vital statistics personnel who collect and summarize abortion data within the United States (*18*).

Variables and Categorization of Data

Each year, CDC sends a suggested template to central health agencies in the United States for compilation of aggregate abortion data among women obtaining legal induced abortions. Aggregate abortion numbers, without individual-level records, are requested for the following variables:

- Age group in years of women obtaining legal induced abortions (<15, 15–19 [age group and by individual year], 20–24, 25–29, 30–34, 35–39, or ≥40)
- Gestational age of pregnancy in completed weeks at the time of abortion (≤6, 7–20 by individual week, or ≥21)
- Race (Black; White; or other including Alaska Native, American Indian, Asian [Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or other Asian], Native Hawaiian or other Pacific Islander [Native Hawaiian, Guamanian or Chamorro, Samoan, or other Pacific Islander], other races, and multiple races), ethnicity (Hispanic or non-Hispanic), and race by ethnicity
- Method type (surgical abortion, intrauterine instillation, medication [nonsurgical] abortion, or hysterectomy or hysterotomy)
- Marital status (married [including currently married or separated] or unmarried [including never married, widowed, or divorced])
- Number of previous live births (zero, one, two, three, or four or more)
- Number of previous induced abortions (zero, one, two, or three or more)
- Residence (the state, jurisdiction, territory, or foreign country in which the women obtaining the abortion lived, or, if additional details are unavailable, in-reporting area versus out-of-reporting area)

In addition, the template provided by CDC requests that aggregate abortion numbers for certain variables be cross-tabulated by a second variable. The cross-tabulations presented in this report include weeks of gestation separately by method type, by age group, and by race and ethnicity.

Beginning with 2014 data, instead of reporting the clinician's estimates of gestational age or estimates of gestational age that were based on last menstrual period, certain areas have reported "probable postfertilization age," "clinician's estimate of gestation based on date of conception," and "probable gestational age" to CDC. To facilitate consistency between data reported as postfertilization age and the data collection practices for gestational age recommended by CDC's National Center for Health Statistics (*19*), 2 weeks were added to probable postfertilization age. This method was used to account for time after last menstrual period until ovulation in a standard 28-day cycle because fertilization occurs around the time of ovulation (*20*). No modifications were made to data reported as clinician's estimate of gestational age that was based on date of conception or data reported as probable gestational age.

In this report, medication and surgical abortions are further categorized by gestational age when available in the categories reported to CDC. Early medication abortion is defined as the administration of medications (typically mifepristone followed by misoprostol) to induce an abortion at ≤9 completed weeks' gestation, consistent with U.S. Food and Drug Administration (FDA) labeling for mifepristone that was implemented in 2016 (*21*). CDC collects information only on the estimated number of weeks (not days) of gestation and acknowledges the conventional use of completed weeks of gestation to describe pregnancy duration; therefore, CDC's category of ≤9 weeks' gestation includes abortions through 9 weeks and 6 days.

Medications (typically serial prostaglandins, sometimes administered after mifepristone) also might be used to induce an abortion at >9 weeks' gestation. Surgical abortions, which include uterine aspiration (i.e., dilation and curettage, aspiration curettage, suction curettage, manual vacuum aspiration, menstrual extraction, or sharp curettage) and dilation and evacuation procedures, are categorized as having been performed at ≤13 weeks' gestation or at >13 weeks' gestation because of differences in surgical technique at these gestational ages (*22*). Finally, because intrauterine instillation is unlikely to be performed early in gestation (*23*), abortions reported to have been performed by intrauterine instillation at ≤12 weeks' gestation are excluded from calculation of the percentage of abortions by known method type and are grouped with unknown type.

Measures of Abortion

Four measures of abortion are presented in this report: 1) the number of abortions in a specific population, 2) the percentage of abortions by selected characteristics, 3) the abortion rate (number of abortions per 1,000 women within a specific population), and 4) the abortion ratio (number of abortions per 1,000 live births within a specific population). Abortion rates adjust for differences in population size. Abortion ratios measure the relative number of pregnancies in a specific population that end in abortion compared with live birth.

U.S. Census Bureau estimates of the resident female population were used as the denominator for calculating abortion rates (*24–33*). Overall abortion rates were calculated from the population of women aged 15–44 years living in the reporting areas that provided continuously reported data. For adolescents aged <15 years, abortion rates were calculated using the number of adolescents aged 13–14 years as the denominator; for women aged ≥40 years, abortion rates were calculated using the number of women aged 40–44 years as the denominator. For the calculation of abortion ratios, live birth data were obtained from CDC natality files and included births to women of all ages living in the reporting areas that provided abortion data (*34,35*). For calculation of the total abortion rates and total abortion ratios only, women with unknown data on selected characteristics (e.g., age, race and ethnicity, and marital status) were distributed according to the distribution of abortions among those with known information on the characteristic. For calculation of totals only, abortions for women with an unknown gestational age of pregnancy but known method type were distributed according to the distribution of abortions among those with known information on method type by gestational age to the following categories: surgical, ≤13 weeks' gestation; surgical, >13 weeks' gestation; medication, ≤9 weeks' gestation; and medication, >9 weeks' gestation.

Data Presentation and Analysis

This report provides aggregate and reporting area–specific abortion numbers, rates, and ratios for the 48 areas that reported to CDC for 2022, which excluded California, Maryland, New Hampshire, and New Jersey. In addition, this report describes characteristics of women who obtained abortions in 2022. The data in this report are presented by the reporting area in which the abortions were performed.

The completeness and quality of data received vary by year, by variable, and by reporting area; this report only describes the characteristics of women obtaining abortions in reporting areas that met CDC reporting standards (i.e., reported at least 20 abortions overall, provided data categorized in accordance with requested variables, and had <15% unknown values for a specific characteristic). Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these values have been suppressed in this report to maintain confidentiality in tables presented by reporting area of occurrence.

The percentage change in abortion measures (number, rate, and ratio of reported abortions) from the most recent past year (2021 to 2022) and during the 10-year period of analysis (2013–2022) were calculated for the 47 areas that reported every year during 2013–2022. The percentage change was also calculated and reported for abortions by age group, weeks of gestation, and early medication abortions (≤9 completed weeks' gestation) for areas that met reporting standards for these variables every year during 2013–2022. As a result, aggregate measures for 2022 in percentage change analyses might differ from the point estimates reported for 2022. These data describe the percentage changes in abortion measures over time and abortion measures among groups for each characteristic. No statistical testing was performed. Comparisons do not imply statistical significance, and lack of comment regarding the difference between values does not imply that no statistically significant difference exists.

Abortion Mortality

CDC has reported data on abortion-related deaths periodically since information on abortion mortality first was included in the 1972 abortion surveillance report (*9,36*). An abortion-related death is defined as a death resulting from a direct complication of an abortion (legal or illegal), an indirect complication caused by a chain of events initiated by an abortion, or an aggravation of a pre-existing condition by the physiologic effects of abortion. An abortion is categorized as legal when it is performed by a licensed clinician within the limits of state or jurisdiction law.

Since 1987, CDC has monitored abortion-related deaths through PMSS, which includes data from all 50 states, the District of Columbia, and New York City (*37*). Sources of data to identify abortion-related deaths have included state or jurisdiction vital records; media reports, including computerized searches of full-text newspaper and other media databases; and individual case reports by public health agencies, including maternal mortality review committees, and any additional data when available. For each death that is possibly related to abortion, CDC requests clinical records and autopsy reports. Two medical epidemiologists independently review these reports to determine the cause of death and whether the death was abortion related. Discrepancies are discussed and resolved by consensus. Each death is categorized by abortion type as legal induced, illegal induced, spontaneous, or unknown type.

This report provides PMSS data on induced abortion–related deaths that occurred in 2021, the most recent year for which PMSS data are available. For 1998–2021, abortion surveillance data reported to CDC cannot be used alone to calculate national case-fatality rates for legal induced abortions (number of legal induced abortion–related deaths per 100,000 reported legal induced abortions in the United States) because nine reporting areas did not report abortion data every year during this period (Alaska, 1998–2000; California, 1998–2021; the District of Columbia, 2016; Louisiana, 2005; Maryland, 2007–2021; New Hampshire, 1998–2021; New Jersey, 2021; Oklahoma, 1998–1999; and West Virginia, 2003–2004). Thus, denominator data for calculation of national legal induced abortion case-fatality rates for 1998–2021 were obtained from a published report by the Guttmacher Institute that includes estimated total numbers of abortions in the United States from a national survey of abortion-providing facilities (*38*). For 2021, denominator data for 2020 were used, the most recent year for which data from the Guttmacher Institute are available. Because rates determined on the basis of a numerator <20 are unstable (*39*), national case-fatality rates for legal induced abortion were calculated for consecutive 5-year periods during 1973–2012 and then for a consecutive 9-year period during 2013–2021.

Top

Results

Total Abortions Reported to CDC by Occurrence

Among the 48 reporting areas that provided data for 2022, a total of 613,383 abortions were reported (Table 1). Of these abortions, 609,360 were from 47 reporting areas that provided data every year during 2013–2022. In 2022, these continuously reporting areas had an abortion rate of 11.2 abortions per 1,000 women aged 15–44 years and an abortion ratio of 199 abortions per 1,000 live births. Among these 47 reporting areas, from 2021 to 2022, the total number of reported abortions decreased 2% (from 622,108 total abortions), the abortion rate decreased 3% (from 11.6 abortions per 1,000 women aged 15–44 years), and the abortion ratio decreased 2% (from 204 abortions per 1,000 live births). From 2013 to 2022, the total number of reported abortions decreased 5% (from 640,154), the abortion rate decreased 10% (from 12.4 abortions per 1,000 women aged 15–44 years), and the abortion ratio increased 1% (from 198 abortions per 1,000 live births) (Figure).

In 2022, reporting areas of occurrence had wide variation in abortion rates (from 0.1 to 28.8 abortions per 1,000 women aged 15–44 years in Missouri and New Mexico, respectively) and abortion ratios (from one to 543 abortions per 1,000 live births in Missouri and New Mexico, respectively) (Table 2). The percentage of abortions obtained by out-of-area residents also varied by reporting area (from 0.8% in Arizona to 68.8% in Kansas).

Age Group, Race and Ethnicity, and Marital Status

Among the 48 areas that reported abortion numbers by women's age for 2022, women in their 20s accounted for more than half of abortions (56.5%) (Table 3). Women aged 20–24 and 25–29 years accounted for the highest percentages of abortions (28.3% and 28.2%, respectively) and had the highest abortion rates (18.1 and 18.7 abortions per 1,000 women aged 20–24 and 25–29 years, respectively). By contrast, adolescents aged <15 years and women aged ≥40 years

accounted for the lowest percentages of abortions (0.2% and 3.6%, respectively) and had the lowest abortion rates (0.4 and 2.5 abortions per 1,000 adolescents aged <15 and women ≥40 years, respectively). However, abortion ratios were highest among adolescents (800 and 389 abortions per 1,000 live births among those aged <15 years and 15–19 years, respectively) and lowest among women aged ≥25 years (194, 133, 134, and 195 abortions per 1,000 live births among those aged 25–29, 30–34, 35–39 years, and ≥40 years, respectively).

Among the 43 reporting areas that provided data each year by women's age for 2013–2022, the highest percentages of abortions and the highest abortion rates occurred among women aged 20–29 years and the lowest percentages of abortions and lowest abortion rates occurred among adolescents aged <15 years and women aged ≥40 years (Table 4). From 2021 to 2022, abortion rates decreased among women aged ≥20 years and did not change among adolescents aged <15 years and adolescents aged 15–19 years.

From 2013 to 2022, abortion rates decreased among all age groups, except women aged 30–34 years for whom it increased. The decrease in the abortion rate was highest among adolescents (33% and 34% for adolescents aged <15 and 15–19 years, respectively) compared with any other age group. From 2021 to 2022, abortion ratios increased for adolescents aged <15 years and 15–19 years and decreased among women aged ≥20 years. From 2013 to 2022, abortion ratios increased among adolescents aged ≤19 years and women aged 20–34 years and decreased among women aged ≥35 years.

Among the 45 areas that reported age by individual year among adolescents for 2022, adolescents aged 18–19 years accounted for the highest percentage (71.6%) of adolescent abortions and had the highest abortion rates (8.6 and 12.4 abortions per 1,000 adolescents aged 18 and 19 years, respectively) (Table 5). Adolescents aged <15 years accounted for the lowest percentage of adolescent abortions (2.6%) and had the lowest abortion rate (0.4 abortions per 1,000 adolescents aged 13–14 years). The abortion ratio for adolescents was highest among those aged <15 years (773 abortions per 1,000 live births) and was lowest among those aged 17–19 years (363, 414, and 343 abortions per 1,000 live births among adolescents aged 17, 18, and 19 years, respectively).

Among the 32 areas that reported race by ethnicity data for 2022, non-Hispanic White (White) women and non-Hispanic Black (Black) women accounted for the highest percentages of all abortions (31.9% and 39.5%, respectively), and Hispanic women and non-Hispanic women in the other race category accounted for lower percentages (21.2% and 7.3%, respectively) (Table 6). White women had the lowest abortion rate (5.7 abortions per 1,000 women aged 15–44 years) and ratio (106 abortions per 1,000 live births), and Black women had the highest abortion rate (24.4 abortions per 1,000 women aged 15–44 years) and ratio (429 abortions per 1,000 live births).

For 2022, among the 36 areas that reported by marital status, 12.3% of women who obtained an abortion were married, and 87.7% were unmarried (Table 7). The abortion ratio was 37 abortions per 1,000 live births for married women and 376 abortions per 1,000 live births for unmarried women.

Previous Live Births and Previous Induced Abortions

For 2022, among the 41 areas that reported the number of previous live births, 40.6%, 24.1%, 19.5%, 9.4%, and 6.5% of abortions reported were among women who had zero, one, two, three, or four or more previous live births, respectively (Table 8). Among the 41 areas that reported the number of previous induced abortions, 56.1%, 24.7%, 10.9%, and 8.2% of abortions reported were among women who had had zero, one, two, or three or more previous induced abortions, respectively (Table 9).

Weeks of Gestation and Method Type

For 2022, among the 41 areas that reported gestational age at the time of abortion, 78.6% of abortions were performed at ≤9 weeks' gestation, and 92.8% were performed at ≤13 weeks' gestation (Table 10). Fewer abortions were performed at 14–20 weeks' gestation (6.1%) or at ≥21 weeks' gestation (1.1%). Among the 36 reporting areas that provided data every year on gestational age for 2013–2022, the percentage of abortions performed at ≤13 weeks' gestation changed from 92.0% in 2013 to 92.5% in 2022 (Table 11). However, within this gestational age range, a shift occurred toward earlier gestational ages, with the percentage of abortions performed at ≤6 weeks' gestation increasing 20% and the percentage of abortions performed at 7–9 weeks' and 10–13 weeks' gestation decreasing 7% and 20%, respectively.

For 2022, among the 47 areas that reported by method type and included medication abortion on their reporting form, 53.3% of abortions were early medication abortions (a nonsurgical abortion at ≤9 weeks' gestation), 35.5% were surgical abortions at ≤13 weeks' gestation, 6.9% were surgical abortions at >13 weeks' gestation, and 4.3% were medication abortions at >9 weeks' gestation; other methods, including intrauterine instillation and hysterectomy or hysterotomy, were rare (<0.1%) (Table 12). During 2013–2022, a total of 39 reporting areas (excludes California, the District of Columbia, Florida, Hawaii, Illinois, Louisiana, Maryland, Missouri, New Hampshire, New Jersey, New Mexico, Tennessee, and Wyoming) provided continuous data and included medication abortion on their reporting form. Among these 39 areas, use of early medication abortion increased 4% from 2021 to 2022 (from 52.1% to 54.0% of abortions) and 129% from 2013 to 2022 (from 23.6% to 54.0% of abortions) (data not shown).

Among the 40 areas that reported abortions categorized by weeks of gestation and method type for 2022, surgical abortion accounted for the highest percentage of abortions at >10 weeks' gestation (Table 13). Surgical abortion accounted for 25.2% of abortions at ≤6 weeks' gestation, 34.4% of abortions at 7–9 weeks' gestation, 72.4% of abortions at 10–13 weeks' gestation, 94.9%–98.1% of abortions at 14–20 weeks' gestation, and 80.0% of abortions at ≥21 weeks' gestation. In contrast, medication abortion accounted for 74.7% of abortions at ≤6 weeks' gestation, 65.6% of abortions at 7–9 weeks' gestation, 27.6% of abortions at 10–13 weeks' gestation, 1.9%–4.8% of abortions at 14–20 weeks' gestation, and 19.4% of abortions at ≥21 weeks' gestation. For each gestational age category as applicable, abortions performed by intrauterine instillation or hysterectomy or hysterotomy were rare (<0.1%–0.4% of abortions).

Weeks of Gestation by Age Group and Race and Ethnicity

In reporting areas that provided data that met CDC reporting standards, abortions that were categorized by weeks of gestation were further categorized by age and by race and ethnicity (Table 14). In every subgroup for these characteristics, the highest percentage of abortions occurred at ≤9 weeks' gestation. In 40 reporting areas, by age, 56.3% of adolescents aged <15 years and 72.5% of adolescents aged 15–19 years obtained an abortion at ≤9 weeks' gestation, compared with ≥77.7% for women aged ≥20 years. Conversely, 18.3% of adolescents aged <15 years and 9.6% of adolescents aged 15–19 years obtained an abortion after 13 weeks' gestation, compared with 6.2%–7.6% for women aged ≥20 years. In 30 reporting areas, by race and ethnicity, 77.1% of abortions obtained by Black women occurred at ≤9 weeks' gestation, compared with 79.4% by non-Hispanic women in the other race category, 80.5% by White women, and 81.8% by Hispanic women. Conversely, 5.3% of abortions obtained by Hispanic women occurred after 13 weeks' gestation, compared with 6.0% by White women, 6.8% by Black women, and 7.2% by non-Hispanic women in the other race category.

Abortion Mortality

Using national PMSS data (*37*), CDC identified five abortion-related deaths for 2021, the most recent year for which data were reviewed for abortion-related deaths (Table 15). Investigation of these cases indicated all deaths were related to legal abortion.

The annual number of deaths related to legal induced abortion has fluctuated from year to year since 1973 (Table 15). During 2013–2021, the national case-fatality rate for legal induced abortion was 0.46 deaths related to legal induced abortions per 100,000 reported legal abortions. This case-fatality rate was lower than the rates for the previous 5-year periods.

Top

Discussion

For 2022, a total of 613,383 abortions were reported to CDC by 48 areas. Among the 47 continuously reporting areas, the abortion rate was 11.2 abortions per 1,000 women aged 15–44 years, and the abortion ratio was 199 abortions per 1,000 live births. From 2021 to 2022, the number of abortions decreased 2%, the abortion rate decreased 3%, and the abortion ratio decreased 2%. Multiple factors influence measures of abortion, including access to health care services and contraception (*40–42*), the availability of abortion providers and clinics (*38,43–47*), changes in legal restrictions and regulations (*48–56*), parental involvement laws (*57,58*), and economic considerations that influence family planning decisions and contraceptive use (*59,60*).

Abortion measures differ by age group. Among areas that reported data continuously by age during 2013–2022, women aged 20–29 years accounted for the highest percentages of abortions and had the highest abortion rates, whereas adolescents aged <15 years accounted for the lowest percentage of abortions and had the lowest abortion rate and adolescents aged <15 years and 15–19 years had the highest abortion ratios. During 2013–2022, women aged ≥40 years accounted for a small percentage of reported abortions (≤3.7%). However, the abortion ratio among women aged ≥40 years continues to be higher than among women aged 25–39 years.

The percentage changes in adolescent abortions described in this report are important for monitoring changes in adolescent pregnancies in the United States. From 2013 to 2022, national birth data indicate that the birth rate for adolescents aged 15–19 years decreased 49% (*35*), and the findings in this report indicate that the abortion rate for the same age group decreased 34%, suggesting a decrease in adolescent pregnancies.

The factors leading to higher abortion rates among certain racial and ethnic minority groups are complex. Race and ethnicity as described in this report are markers not drivers of differences in abortion rates. In addition to disparities in rates of unintended pregnancies (*61*), structural factors, including unequal access to quality family planning services (*62*), economic inequities, and mistrust of the medical system (*63*), can contribute to observed differences. As in previous years, abortion rates and ratios differed across racial and ethnic groups. In 2022, compared with White women, abortion rates and ratios were 4.3 and 4.0 times higher among Black women and 2.0 and 1.6 times higher among Hispanic women. Similar differences by race and ethnicity have been demonstrated in other U.S.-based studies (*2,10–13*).

During 2022, approximately four of five abortions occurred early in gestation (≤9 weeks), when the risks for complications are lowest (*64–67*). During the past 10 years, this percentage increased from 75.0% in 2013 to 78.9% in 2022. Moreover, among areas that reported abortions at ≤13 weeks' gestation by individual week, the distribution of abortions by gestational age continued to shift toward earlier weeks of gestation, with the percentage of early abortions performed at ≤6 weeks' gestation increasing from 34.8% in 2013 to 41.6% in 2022. Previous research indicates that the distribution of abortions by gestational age differs by various sociodemographic characteristics (*68–70*). In this report, the percentage of adolescents aged ≤19 years who obtained abortions at >13 weeks' gestation was higher than the percentage of women aged ≥20 years. The gestational age when abortions are performed can be influenced by multiple factors, including state or jurisdiction abortion restrictions, accurate estimation of gestational age, income level, age, and presence of pregnancy-related health conditions (*48,67,69–74*).

Changes in clinical practices have facilitated the trend of obtaining abortions earlier in pregnancy. Research conducted in the United States during the 1970s indicated that surgical abortion procedures performed at ≤6 weeks' gestation, compared with 7–12 weeks' gestation, were less likely to result in successful termination of the pregnancy (*75*). However, subsequent advances in technology (e.g., improved transvaginal ultrasonography and sensitivity of pregnancy tests) have allowed early surgical abortions to be performed with completion rates exceeding 97% (*76–79*). Likewise, the development of early medication abortion regimens has allowed for abortions to be performed early in gestation, with completion rates for regimens that combine mifepristone and misoprostol reaching 96%–98% (*79–83*).

Trends for early medication abortions are reported to monitor any changes in clinical practice that might have occurred with the accumulation of evidence on the safety and effectiveness of medication abortion beyond 63 days of gestation (8 completed weeks' gestation) (*84*), changes in professional practice guidelines (*85,86*), and the 2016 FDA extension of the gestational age limit for the use of mifepristone for early medication abortion from 63 days to 70 days (9 completed weeks' gestation) (*87*). Among abortions occurring at ≤9 weeks' gestation in 2022, approximately two thirds (70.2%) were reported as early medication abortions. In 2022, the most common method among abortions reported overall was early medication abortion at ≤9 weeks' gestation (53.3%). Among continuously reporting areas that reported by method type and included medication abortion on their reporting form, the percentage of all abortions performed by early medication abortion increased 129% from 2013 to 2022 and increased 4% from 2021 to 2022.

Because the annual number of deaths related to legal induced abortion is small and statistically unstable, case-fatality rates were calculated for consecutive 5-year periods during 1973–2012 and then for a consecutive 9-year period during 2013–2021. The national case-fatality rate for legal induced abortion was 0.46 per 100,000 abortions during 2013–2021. Since 1978, all rates for the preceding 5-year periods have been <1 death per 100,000 abortions, demonstrating the low risk for death associated with legal induced abortion.

Top

Limitations

The findings in this report are subject to at least five limitations. First, because reporting to CDC is voluntary and reporting requirements vary by the individual reporting areas (*16,17*), CDC is unable to report the total number of abortions performed in the United States. Of the 52 areas from which CDC requested data for 2022, California, Maryland, New Hampshire, and New Jersey did not submit abortion data. In 2020, the most recent year for which data are available through the Guttmacher Institute's national survey of abortion-providing facilities, abortions performed in these states accounted for approximately 20% of all abortions in the United States (*38*). CDC receives aggregated data from the central health agencies of reporting areas, which might result in different estimates than reported by the Guttmacher Institute. Completeness of reporting might vary by reporting area. Whereas most reporting areas have a legal requirement to submit a report for every abortion performed (*16*), adherence to this requirement might vary (*17*). Access to telehealth services for abortion varies by state or jurisdiction (*47*) and reporting of abortions that occur using telehealth services also might vary by reporting area.

Second, many states and jurisdictions use abortion reporting forms that differ from the technical guidance that NAPHSIS developed with technical assistance from CDC. Consequently, certain reporting areas do not collect all variables requested by CDC (e.g., race and ethnicity), do not collect or report all variables for out-of-area residents (e.g., Nevada), or do not report the data in a manner consistent with this guidance (e.g., gestational age). Missing demographic information can reduce the extent to which the statistics in this report represent women who have had abortions. Only 32 reporting areas reported race and ethnicity data to CDC that met CDC's reporting standards. Certain areas that either do not report to CDC (e.g., California) or do not report race and ethnicity data (e.g., Illinois) have sufficiently large populations of racial and ethnic minority groups that the absence of data from these areas reduces the representativeness of CDC data for these variables. In addition, because of the variability in data collection for race and ethnicity among reporting areas, data for specific racial and ethnic groups beyond Black, White, and Hispanic are not requested or reported. In addition, certain areas collect gestational age data that are based on estimated date of conception or probable postfertilization age, which are not consistent with medical conventions for gestational age reporting. Without medical guidance on how to report these data, the validity and reliability of gestational age for these reporting areas is uncertain.

Third, abortion data are compiled and reported to CDC by the central health agency of the reporting area in which the abortion was performed rather than the reporting area in which the person lived. Thus, the available population (*24–33*) and birth data (*34,35*), which are organized by the states or jurisdictions in which women live, might differ from the population of women who undergo abortions in a specific reporting area. This likely results in an overestimation of abortion measures for reporting areas in which a higher percentage of abortions are obtained by out-of-area residents and an underestimation of abortions for reporting areas where residents more frequently obtain abortions out of area. Limited abortion services, stringent regulatory requirements for obtaining an abortion, or geographic proximity to services in another state or jurisdiction might influence where women obtain abortion services (*88,89*). Studies have demonstrated an increase in out-of-area abortions for residents of states with legal restrictions for abortion (*53,90*).

Fourth, in this report, the presentations of percentage change for abortions by variables (e.g., weeks of gestation) are limited to the aggregate of the 47 jurisdictions that met reporting standards for every year during 2013–2022. This approach allows for assessment of changes in continuously reporting areas; however, specific jurisdictions' patterns might differ from aggregate 10-year or year-to-year comparisons.

Finally, CDC reporting of sociodemographic characteristics of women obtaining abortions is limited to data collected on state or jurisdiction reporting forms. Therefore, the examination of additional demographic variables (e.g., income and education) is not possible.

Top

Public Health Implications

Ongoing surveillance of legal induced abortion is important for three reasons. First, abortion surveillance can be used to help evaluate programs aimed at promoting equitable access to patient-centered contraceptive care in the United States to reduce unintended pregnancies. Up to 42% of pregnancies in the United States are unintended (*61*), and use of effective contraception is a strategy to reduce unintended pregnancy (*91*). Efforts to improve contraceptive access that consider patient perspectives and remove barriers (e.g., cost) have been associated with declines in the rate of abortion (*40–42*). Providing contraception at low or no cost can increase contraceptive access and use (*92–94*). Improvements in provider

reimbursement and training, patient-centered counseling, youth-friendly services, and client awareness of available contraceptive methods also might help to improve contraceptive access (*95–97*), ensure equitable access to patient-centered contraceptive care, and promote equitable reproductive health in the United States (*98*). Second, routine abortion surveillance can be used to assess changes in clinical practice patterns over time. Information in this report on the number of abortions performed through different methods (e.g., medication or surgical) and at different gestational ages provides the denominator data that are necessary for analyses of the relative safety of abortion practices (*99*). Finally, information on the number of pregnancies ending in abortion is used in conjunction with data on births and fetal losses to estimate the number of pregnancies in the United States and determine rates for various outcomes of public health importance (*61*).

Top

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Top

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Top

Conflicts of Interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

Top

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Top

TABLE 1. Number, rate,* and ratio† of reported abortions — selected reporting areas, United States, 2013–2022

Year	Selected reporting areas§	Continuously reporting areas¶		
	No.	No.	Rate	Ratio
2013	664,435	640,154	12.4	198
2014	652,639	625,668	12.0	190
2015	638,169	613,911	11.8	187
2016	623,471	599,001	11.5	184
2017	612,719	587,611	11.2	184
2018	619,591	591,884	11.2	188
2019	629,898	603,168	11.4	194
2020	620,327	592,939	11.1	197
2021	625,978	622,108	11.6	204
2022	613,383	609,360	11.2	199

* Number of abortions per 1,000 women aged 15–44 years.

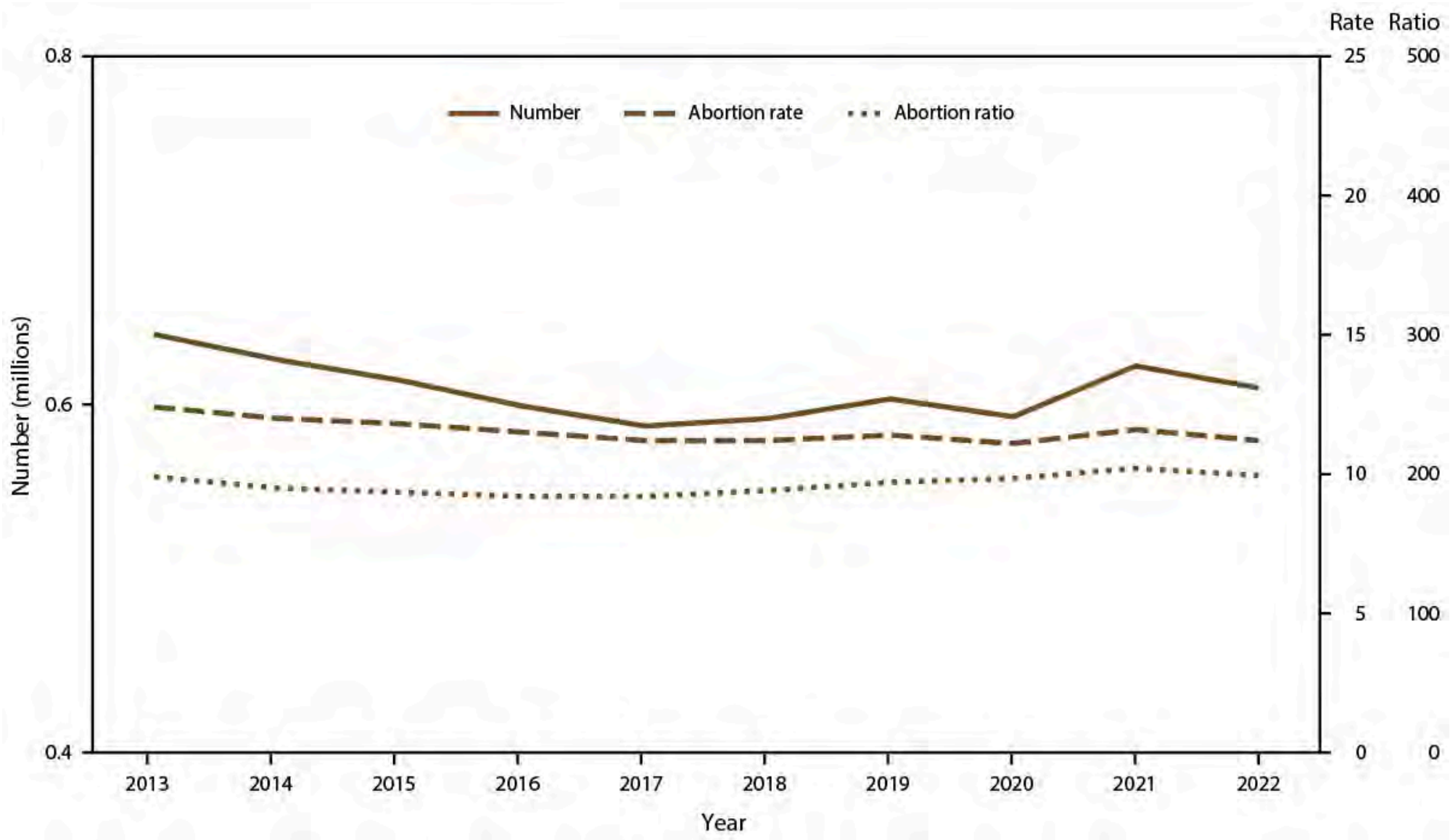
† Number of abortions per 1,000 live births.

§ For each specific year, excludes reporting areas that did not report that year's abortion numbers to CDC: California (2013–2022), District of Columbia (2016), Maryland (2013–2022), New Hampshire (2013–2022), and New Jersey (2021–2022).

¶ For all years, excludes reporting areas that did not report abortion numbers every year during the analysis period: California, District of Columbia, Maryland, New Hampshire, and New Jersey.

Top

FIGURE. Number, rate,* and ratio† of abortions performed, by year — selected reporting areas,§ United States, 2013–2022



* Number of abortions per 1,000 women aged 15–44 years.

† Number of abortions per 1,000 live births.

§ Data are for 47 reporting areas; excludes California, District of Columbia, Maryland, New Hampshire, and New Jersey.

Top

TABLE 2. Number, rate,* and ratio† of reported abortions, by reporting area of occurrence and number of abortions obtained by out-of-area residents§ — United States, 2022¶

Area	Abortions reported by area of occurrence**			Abortions obtained by out-of-area residents
	No.	Rate	Ratio	No. (%)
Alabama	3,777	3.8	65	794 (21.0)
Alaska	1,247	8.6	133	15 (1.2)
Arizona	11,530	8.1	147	97 (0.8)
Arkansas	1,621	2.8	46	437 (27.0)
Colorado	14,154	11.7	227	3,924 (27.7)

Area	Abortions reported by area of occurrence**			Abortions obtained by out-of-area residents
	No.	Rate	Ratio	No. (%)
Connecticut	11,121	16.0	315	523 (4.7)
Delaware	2,445	13.0	226	254 (10.4)
District of Columbia	4,023	22.4	498	2,696 (67.0)
Florida	82,581	20.5	368	6,721 (8.1)
Georgia	38,820	17.2	308	8,005 (20.6)
Hawaii	1,970	7.5	127	45 (2.3)
Idaho	1,027	2.7	46	49 (4.8)
Illinois	56,457	22.8	440	16,849 (29.8)
Indiana	9,530	7.1	120	1,828 (19.2)
Iowa	4,068	6.7	111	759 (18.7)
Kansas	12,317	21.6	358	8,475 (68.8)
Kentucky	2,550	3.0	49	419 (16.4)
Louisiana	4,570	5.0	81	1,662 (36.4)
Maine	2,225	9.1	184	124 (5.6)
Massachusetts	17,757	12.6	259	920 (5.2)
Michigan	30,120	15.9	294	2,758 (9.2)
Minnesota	12,175	11.1	190	2,009 (16.5)
Mississippi	2,286	3.9	66	648 (28.3)
Missouri	88	0.1	1	16 (18.2)
Montana	1,702	8.1	152	164 (9.6)
Nebraska	2,547	6.7	105	532 (20.9)
Nevada	11,957	19.2	360	1,578 (13.2)
New Mexico	11,735	28.8	543	7,323 (62.4)
New York	72,710	18.7	350	4,183 (5.8)††
New York City	46,373	26.2	498	4,463 (9.6)

Area	Abortions reported by area of occurrence**			Abortions obtained by out-of-area residents
	No.	**Rate**	**Ratio**	**No. (%)**
New York State	26,337	12.5	230	2,052 (7.8)
North Carolina	40,037	19.0	329	11,716 (29.3)
North Dakota	754	4.9	79	222 (29.4)
Ohio	18,499	8.3	144	1,287 (7.0)
Oklahoma	2,160	2.7	45	1,257 (58.2)
Oregon	8,672	10.4	220	1,036 (11.9)
Pennsylvania	34,838	14.2	267	3,311 (9.5)
Rhode Island	1,383	6.4	135	193 (14.0)
South Carolina	7,276	7.2	126	1,709 (23.5)
South Dakota	137	0.8	12	14 (10.2)
Tennessee	6,452	4.6	78	1,333 (20.7)
Texas	17,514	2.8	45	302 (1.7)
Utah	3,824	5.1	84	215 (5.6)
Vermont	1,108	9.2	208	217 (19.6)
Virginia[§§]	16,722	9.7	175	2,454 (14.7)
Washington	20,193	12.9	242	1,440 (7.1)
West Virginia	831	2.7	49	182 (21.9)
Wisconsin	3,333	3.0	56	54 (1.6)
Wyoming	540	4.9	89	166 (30.7)
Total	**613,383**	**NA**	**NA**	**NA**

Abbreviation: NA = not applicable.

* Number of abortions per 1,000 women aged 15–44 years.

† Number of abortions per 1,000 live births.

§ Additional details on the reporting area in which abortions were provided, cross-tabulated by the area of residence, are available at https://www.cdc.gov/reproductive-health/data-statistics/abortion-surveillance-findings-reports.html.

¶ Data from 48 reporting areas; excludes four reporting areas (California, Maryland, New Hampshire, and New Jersey) that did not report.

** The total abortions include those with known and unknown residence status.

†† Residents of New York State who had abortions in New York City and residents of New York City who had abortions in

New York State were excluded from the number and percentage of abortions obtained by out-of-area residents in New York.

[§§] Data reported from facilities physically situated in state only.

Top

TABLE 3. Number and percentage of reported abortions, by known age group and reporting area of occurrence — selected reporting areas,[*] United States, 2022

Area	Age group, yrs							Total abortions reported by known age
	<15	15–19	20–24	25–29	30–34	35–39	≥40	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Alabama	11 (0.3)	366 (9.7)	1,240 (32.8)	1,061 (28.1)	691 (18.3)	300 (7.9)	106 (2.8)	**3,775 (99.9)**
Alaska	5 (0.4)	123 (9.9)	389 (31.2)	320 (25.7)	235 (18.9)	136 (10.9)	38 (3.0)	**1,246 (99.9)**
Arizona	12 (0.1)	1,095 (9.5)	3,562 (30.9)	3,188 (27.6)	2,093 (18.2)	1,165 (10.1)	415 (3.6)	**11,530 (100.0)**
Arkansas	9 (0.6)	167 (10.3)	500 (30.9)	479 (29.6)	302 (18.7)	125 (7.7)	37 (2.3)	**1,619 (99.9)**
Colorado	47 (0.3)	1,439 (10.2)	4,434 (31.4)	3,801 (26.9)	2,582 (18.3)	1,345 (9.5)	483 (3.4)	**14,131 (99.8)**
Connecticut	22 (0.2)	1,009 (9.1)	3,036 (27.3)	3,021 (27.2)	2,322 (20.9)	1,290 (11.6)	410 (3.7)	**11,110 (99.9)**
Delaware	6 (0.2)	238 (9.7)	721 (29.5)	685 (28.0)	474 (19.4)	243 (9.9)	78 (3.2)	**2,445 (100.0)**
District of Columbia	12 (0.3)	427 (10.6)	1,147 (28.5)	1,182 (29.4)	764 (19.0)	364 (9.1)	124 (3.1)	**4,020 (99.9)**
Florida	137 (0.2)	5,756 (7.0)	22,427 (27.2)	23,231 (28.2)	17,684 (21.5)	9,718 (11.8)	3,369 (4.1)	**82,322 (99.7)**
Georgia	74 (0.2)	2,750 (7.1)	10,684 (27.5)	11,634 (30.0)	8,339 (21.5)	3,957 (10.2)	1,382 (3.6)	**38,820 (100.0)**
Hawaii	—[¶]	181 (9.2)	552 (28.0)	526 (26.7)	382 (19.4)	228 (11.6)	—[¶]	**1,970 (100.0)**
Idaho	—[¶]	125 (12.2)	349 (34.0)	277 (27.0)	155 (15.1)	94 (9.2)	—[¶]	**1,027 (100.0)**
Illinois**	75 (0.2)	3,303 (8.5)	11,189 (28.8)	11,593 (29.9)	7,827 (20.2)	3,698 (9.5)	1,128 (2.9)	**38,813 (99.6)**

Area	Age group, yrs							Total abortions reported by known age
	<15	15–19	20–24	25–29	30–34	35–39	≥40	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Indiana	22 (0.2)	840 (8.8)	2,910 (30.5)	2,677 (28.1)	1,849 (19.4)	893 (9.4)	339 (3.6)	**9,530 (100.0)**
Iowa	13 (0.3)	420 (10.3)	1,277 (31.4)	1,048 (25.8)	746 (18.4)	430 (10.6)	129 (3.2)	**4,063 (99.9)**
Kansas	35 (0.3)	1,159 (9.4)	3,908 (31.7)	3,322 (27.0)	2,232 (18.1)	1,278 (10.4)	383 (3.1)	**12,317 (100.0)**
Kentucky	10 (0.4)	201 (7.9)	831 (32.6)	691 (27.1)	498 (19.5)	245 (9.6)	74 (2.9)	**2,550 (100.0)**
Louisiana	20 (0.4)	425 (9.3)	1,379 (30.2)	1,250 (27.4)	904 (19.8)	476 (10.4)	116 (2.5)	**4,570 (100.0)**
Maine	6 (0.3)	210 (9.5)	596 (26.9)	589 (26.6)	457 (20.6)	271 (12.2)	89 (4.0)	**2,218 (99.7)**
Massachusetts	32 (0.2)	1,392 (7.8)	4,622 (26.0)	4,710 (26.5)	3,897 (22.0)	2,232 (12.6)	863 (4.9)	**17,748 (99.9)**
Michigan	85 (0.3)	2,328 (7.8)	8,297 (27.7)	8,766 (29.3)	6,742 (22.5)	2,848 (9.5)	867 (2.9)	**29,933 (99.4)**
Minnesota	26 (0.2)	1,117 (9.2)	3,431 (28.2)	3,277 (26.9)	2,523 (20.7)	1,338 (11.0)	454 (3.7)	**12,166 (99.9)**
Mississippi	7 (0.3)	200 (8.7)	738 (32.3)	705 (30.8)	416 (18.2)	171 (7.5)	49 (2.1)	**2,286 (100.0)**
Missouri	—[¶]	—[¶]	18 (20.5)	21 (23.9)	20 (22.7)	15 (17.0)	10 (11.4)	**88 (100.0)**
Montana	6 (0.4)	189 (11.1)	490 (28.8)	444 (26.1)	313 (18.4)	186 (10.9)	74 (4.3)	**1,702 (100.0)**
Nebraska	7 (0.3)	270 (10.6)	850 (33.4)	676 (26.5)	419 (16.5)	252 (9.9)	73 (2.9)	**2,547 (100.0)**
Nevada[††]	11 (0.1)	964 (8.4)	3,061 (26.7)	3,206 (28.0)	2,410 (21.1)	1,298 (11.3)	494 (4.3)	**11,444 (95.7)**
New Mexico	48 (0.4)	1,234 (10.7)	3,528 (30.7)	3,014 (26.2)	2,048 (17.8)	1,248 (10.9)	368 (3.2)	**11,488 (97.9)**

Area	Age group, yrs							Total abortions reported by known age
	<15	15–19	20–24	25–29	30–34	35–39	≥40	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
New York	169 (0.2)	5,941 (8.2)	19,084 (26.3)	20,173 (27.8)	15,544 (21.4)	8,626 (11.9)	3,132 (4.3)	**72,669 (99.9)**
New York City	89 (0.2)	3,465 (7.5)	11,748 (25.3)	13,067 (28.2)	10,140 (21.9)	5,733 (12.4)	2,131 (4.6)	**46,373 (100.0)**
New York State	80 (0.3)	2,476 (9.4)	7,336 (27.9)	7,106 (27.0)	5,404 (20.6)	2,893 (11.0)	1,001 (3.8)	**26,296 (99.8)**
North Carolina	82 (0.2)	3,154 (8.0)	11,508 (29.3)	11,532 (29.4)	7,974 (20.3)	3,864 (9.8)	1,172 (3.0)	**39,286 (98.1)**
North Dakota	6 (0.8)	90 (11.9)	215 (28.5)	191 (25.3)	160 (21.2)	79 (10.5)	13 (1.7)	**754 (100.0)**
Ohio	42 (0.2)	1,494 (8.1)	5,455 (29.5)	5,325 (28.8)	3,791 (20.5)	1,825 (9.9)	567 (3.1)	**18,499 (100.0)**
Oklahoma	12 (0.6)	244 (11.3)	732 (34.0)	574 (26.6)	353 (16.4)	190 (8.8)	50 (2.3)	**2,155 (99.8)**
Oregon	12 (0.1)	894 (10.3)	2,561 (29.5)	2,336 (26.9)	1,636 (18.9)	922 (10.6)	309 (3.6)	**8,670 (100.0)**
Pennsylvania	76 (0.2)	2,724 (7.8)	9,351 (26.8)	10,107 (29.0)	7,591 (21.8)	3,765 (10.8)	1,224 (3.5)	**34,838 (100.0)**
Rhode Island	—[¶]	114 (8.2)	362 (26.2)	368 (26.6)	294 (21.3)	190 (13.7)	—[¶]	**1,383 (100.0)**
South Carolina	19 (0.3)	641 (8.8)	2,072 (28.5)	2,087 (28.7)	1,457 (20.0)	759 (10.4)	241 (3.3)	**7,276 (100.0)**
South Dakota	—[¶]	—[¶]	51 (37.2)	32 (23.4)	25 (18.2)	16 (11.7)	—[¶]	**137 (100.0)**
Tennessee	14 (0.2)	513 (8.0)	1,846 (28.6)	1,979 (30.7)	1,318 (20.4)	584 (9.1)	197 (3.1)	**6,451 (100.0)**
Texas	14 (0.1)	1,242 (7.1)	5,154 (29.4)	5,101 (29.1)	3,566 (20.4)	1,835 (10.5)	602 (3.4)	**17,514 (100.0)**
Utah	8 (0.2)	469 (12.3)	1,313 (34.3)	928 (24.3)	623 (16.3)	350 (9.2)	133 (3.5)	**3,824 (100.0)**

Area	Age group, yrs							Total abortions reported by known age
	<15	15–19	20–24	25–29	30–34	35–39	≥40	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Vermont	—[¶]	100 (9.0)	320 (28.9)	274 (24.7)	243 (21.9)	120 (10.8)	—[¶]	**1,108 (100.0)**
Virginia[§§]	38 (0.2)	1,155 (6.9)	4,515 (27.0)	4,767 (28.5)	3,498 (20.9)	2,007 (12.0)	739 (4.4)	**16,719 (100.0)**
Washington	39 (0.2)	2,063 (10.2)	5,669 (28.1)	5,268 (26.1)	3,884 (19.2)	2,388 (11.8)	871 (4.3)	**20,182 (99.9)**
West Virginia	—[¶]	92 (11.1)	268 (32.3)	232 (28.0)	149 (18.0)	60 (7.2)	—[¶]	**830 (99.9)**
Wisconsin	13 (0.4)	337 (10.1)	1,085 (32.6)	878 (26.3)	619 (18.6)	315 (9.5)	86 (2.6)	**3,333 (100.0)**
Wyoming	0 (0.0)	41 (7.6)	141 (26.1)	143 (26.5)	115 (21.3)	70 (13.0)	30 (5.6)	**540 (100.0)**
Total	**1,292 (0.2)**	**49,251 (8.3)**	**167,868 (28.3)**	**167,689 (28.2)**	**122,164 (20.6)**	**63,809 (10.7)**	**21,573 (3.6)**	**593,646 (99.6)[¶¶]**
Abortion rate* **	**0.4**	**5.6**	**18.1**	**18.7**	**13.0**	**7.1**	**2.5**	**NA**
Abortion ratio[†††]	**800**	**389**	**301**	**194**	**133**	**134**	**195**	**NA**

Abbreviation: NA = not applicable.

* Data from 48 reporting areas; excludes four reporting areas (California, Maryland, New Hampshire, and New Jersey) that did not report, did not report by age, or did not meet reporting standards.

[†] Percentages for the individual component categories might not add to 100% because of rounding.

[§] Percentage is calculated as the number of abortions reported by known age divided by the sum of abortions reported by known and unknown age. Values ≥99.95% are rounded to 100.0%.

[¶] Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these small values have been suppressed.

** Includes residents only.

[††] For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

[§§] Data reported from facilities physically situated in state only.

[¶¶] Percentage is based on a total of 613,383 abortions reported among the areas that met reporting standards for age; reporting standards for age were applied to abortions for residents of Illinois only.

*** Number of abortions obtained by women in a specific age group per 1,000 women in that same age group. Adolescents aged 13–14 years were used as the denominator for the group of adolescents aged <15 years, and women aged 40–44 years were used as the denominator for the group of women aged ≥40 years. For the total abortion rate only, abortions for women of unknown age were distributed according to the distribution of abortions among women of known age.

[†††] Number of abortions obtained by women in a specific age group per 1,000 live births to women in that same age group. For the total abortion ratio only, abortions for women of unknown age were distributed according to the distribution of abortions among women of known age.

Top

TABLE 4. Percentage, rate,[*] and ratio[†] of reported abortions, by known age group and year — selected United States, 2013–2022

Age group, yrs	Year									
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Reported abortions by known age (%)										
<15	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.1
15–19	11.5	10.4	9.8	9.4	9.1	8.8	8.7	8.3	8.2	8.5
20–24	32.7	32.2	31.2	30.1	29.4	28.6	27.9	28.2	28.5	28.
25–29	25.9	26.7	27.6	28.5	28.9	29.3	29.3	29.3	28.7	28.
30–34	16.8	17.2	17.7	18.0	18.3	18.8	19.4	19.7	20.2	20.
35–39	9.2	9.6	10.0	10.3	10.5	10.7	10.8	10.6	10.6	10.
≥40	3.6	3.6	3.6	3.6	3.6	3.5	3.7	3.6	3.5	3.(
Abortion rate										
<15	0.6	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4
15–19	8.2	7.3	6.7	6.2	5.9	5.8	5.8	5.5	5.4	5.4
20–24	21.8	20.8	19.9	19.0	18.3	18.1	18.1	18.1	18.6	17.
25–29	18.1	17.9	17.8	17.7	17.3	17.5	17.8	17.7	18.3	17.
30–34	11.8	11.6	11.7	11.6	11.5	11.8	12.3	12.1	12.5	12.
35–39	7.0	7.0	7.0	6.9	6.7	6.8	7.0	6.7	6.8	6.(
≥40	2.6	2.5	2.5	2.5	2.5	2.5	2.6	2.4	2.4	2.3
Abortion ratio										
<15	771	737	690	724	788	846	858	809	780	79
15–19	297	289	286	292	300	315	330	338	366	37
20–24	260	253	249	247	248	254	259	273	290	28
25–29	167	164	165	167	170	177	182	189	189	18

Age group, yrs	Year									
	2013	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
30–34	122	116	115	113	114	119	125	127	127	12
35–39	149	145	141	137	135	136	138	135	132	12
≥40	247	240	230	221	213	209	216	207	198	18
Total no.¶	**544,986**	**531,041**	**520,602**	**508,565**	**497,249**	**500,974**	**508,955**	**502,481**	**514,695**	**498,**

Abbreviation: NA = not applicable.

* Number of abortions obtained by women in a specific age group per 1,000 women in that same age group. Adolescents aged 13–14 years were used as the denominator for the group of adolescents aged <15 years, and women aged 40–44 years were used as the denominator for the group of women aged ≥40 years. Abortions for women of unknown age were distributed according to the distribution of abortions among women of known age.

† Number of abortions obtained by women in a specific age group per 1,000 live births to women in that same age group. Abortions for women of unknown age were distributed according to the distribution of abortions among women of known age.

§ Data from 43 reporting areas; excludes nine reporting areas (California, District of Columbia, Florida, Maine, Maryland, New Hampshire, New Jersey, Tennessee, and Wyoming) that did not report, did not report by age, or did not meet reporting standards for ≥1 year.

¶ By year, the total number of abortions represent 99.5%–99.7% of all abortions reported to CDC among the areas that met reporting standards for age during 2013–2022; reporting standards for age were applied to abortions for residents of Illinois only during 2013–2019 and 2021–2022.

Top

TABLE 5. Number and percentage of reported abortions among adolescents, by known age and reporting area of occurrence — selected reporting areas,* United States, 2022

	Age, yrs						
	<15	**15**	**16**	**17**	**18**	**19**	**Total no.**
Area	**No. (%)†**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	
Alabama	11 (2.9)	24 (6.4)	33 (8.8)	39 (10.3)	109 (28.9)	161 (42.7)	**377**
Alaska	5 (3.9)	7 (5.5)	10 (7.8)	18 (14.1)	33 (25.8)	55 (43.0)	**128**
Arizona	12 (1.1)	39 (3.5)	71 (6.4)	129 (11.7)	369 (33.3)	487 (44.0)	**1,107**
Arkansas	9 (5.1)	8 (4.5)	11 (6.3)	27 (15.3)	54 (30.7)	67 (38.1)	**176**
Colorado	47 (3.2)	63 (4.2)	139 (9.4)	211 (14.2)	434 (29.2)	592 (39.8)	**1,486**
Delaware	6 (2.5)	8 (3.3)	24 (9.8)	43 (17.6)	68 (27.9)	95 (38.9)	**244**

Area	Age, yrs						Total no.
	<15	15	16	17	18	19	
	No. (%)†	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
District of Columbia	12 (2.7)	14 (3.2)	61 (13.9)	103 (23.5)	91 (20.7)	158 (36.0)	**439**
Florida	137 (2.3)	208 (3.5)	423 (7.2)	708 (12.0)	1,730 (29.4)	2,687 (45.6)	**5,893**
Georgia	74 (2.6)	122 (4.3)	191 (6.8)	346 (12.3)	840 (29.7)	1,251 (44.3)	**2,824**
Hawaii	—§	—§	—§	—§	—§	—§	**—§**
Idaho	—§	—§	—§	—§	—§	—§	**—§**
Indiana	22 (2.6)	37 (4.3)	70 (8.1)	100 (11.6)	278 (32.3)	355 (41.2)	**862**
Iowa	13 (3.0)	22 (5.1)	30 (6.9)	74 (17.1)	119 (27.5)	175 (40.4)	**433**
Kansas	35 (2.9)	60 (5.0)	78 (6.5)	127 (10.6)	371 (31.1)	523 (43.8)	**1,194**
Kentucky	10 (4.7)	9 (4.3)	14 (6.6)	35 (16.6)	58 (27.5)	85 (40.3)	**211**
Louisiana	20 (4.5)	29 (6.5)	45 (10.1)	44 (9.9)	110 (24.7)	197 (44.3)	**445**
Maine	6 (2.8)	13 (6.0)	15 (6.9)	36 (16.7)	60 (27.8)	86 (39.8)	**216**
Massachusetts	32 (2.2)	54 (3.8)	129 (9.1)	195 (13.7)	399 (28.0)	615 (43.2)	**1,424**
Michigan	85 (3.5)	98 (4.1)	196 (8.1)	338 (14.0)	702 (29.1)	994 (41.2)	**2,413**
Minnesota	26 (2.3)	45 (3.9)	87 (7.6)	148 (12.9)	355 (31.1)	482 (42.2)	**1,143**
Mississippi	7 (3.4)	14 (6.8)	18 (8.7)	25 (12.1)	56 (27.1)	87 (42.0)	**207**
Missouri	—§	—§	—§	—§	—§	—§	**—§**
Montana	6 (3.1)	8 (4.1)	16 (8.2)	27 (13.8)	53 (27.2)	85 (43.6)	**195**
Nebraska	7 (2.5)	13 (4.7)	21 (7.6)	45 (16.2)	82 (29.6)	109 (39.4)	**277**
Nevada¶	11 (1.1)	50 (5.1)	75 (7.7)	156 (16.0)	272 (27.9)	411 (42.2)	**975**
New Mexico	48 (3.7)	66 (5.1)	115 (9.0)	208 (16.2)	352 (27.5)	493 (38.5)	**1,282**
New York	169 (2.8)	272 (4.5)	581 (9.5)	957 (15.7)	1,688 (27.6)	2,443 (40.0)	**6,110**
New York City	89 (2.5)	164 (4.6)	334 (9.4)	547 (15.4)	973 (27.4)	1,447 (40.7)	**3,554**
New York State	80 (3.1)	108 (4.2)	247 (9.7)	410 (16.0)	715 (28.0)	996 (39.0)	**2,556**
North Carolina	82 (2.5)	146 (4.5)	262 (8.1)	393 (12.1)	1,016 (31.4)	1,337 (41.3)	**3,236**

Area	Age, yrs						Total no.
	<15	15	16	17	18	19	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
North Dakota	6 (6.3)	—[§]	—[§]	13 (13.5)	33 (34.4)	34 (35.4)	**96**
Ohio	42 (2.7)	76 (4.9)	124 (8.1)	213 (13.9)	440 (28.6)	641 (41.7)	**1,536**
Oklahoma	12 (4.7)	9 (3.5)	17 (6.6)	21 (8.2)	97 (37.9)	100 (39.1)	**256**
Oregon	12 (1.3)	28 (3.1)	68 (7.5)	138 (15.2)	292 (32.2)	368 (40.6)	**906**
Pennsylvania	76 (2.7)	147 (5.3)	207 (7.4)	331 (11.8)	828 (29.6)	1,211 (43.3)	**2,800**
Rhode Island	—[§]	—[§]	—[§]	—[§]	—[§]	—[§]	**—[§]**
South Carolina	19 (2.9)	28 (4.2)	50 (7.6)	125 (18.9)	211 (32.0)	227 (34.4)	**660**
South Dakota	—[§]	—[§]	—[§]	—[§]	—[§]	—[§]	**—[§]**
Tennessee	14 (2.7)	16 (3.0)	47 (8.9)	58 (11.0)	158 (30.0)	234 (44.4)	**527**
Texas	14 (1.1)	42 (3.3)	76 (6.1)	145 (11.5)	362 (28.8)	617 (49.1)	**1,256**
Utah	8 (1.7)	18 (3.8)	32 (6.7)	51 (10.7)	165 (34.6)	203 (42.6)	**477**
Vermont	—[§]	—[§]	—[§]	—[§]	—[§]	—[§]	**—[§]**
Virginia**	38 (3.2)	54 (4.5)	79 (6.6)	142 (11.9)	326 (27.3)	554 (46.4)	**1,193**
Washington	39 (1.9)	94 (4.5)	199 (9.5)	317 (15.1)	594 (28.3)	859 (40.9)	**2,102**
West Virginia	—[§]	—[§]	—[§]	—[§]	—[§]	—[§]	**—[§]**
Wyoming	0 (0.0)	—[§]	—[§]	—[§]	15 (36.6)	22 (53.7)	**41**
Total	**1,182 (2.6)**	**1,973 (4.3)**	**3,683 (8.0)**	**6,178 (13.5)**	**13,408 (29.3)**	**19,360 (42.3)**	**45,784**
Abortion rate[††]	**0.4**	**1.2**	**2.3**	**4.0**	**8.6**	**12.4**	**NA**
Abortion ratio[§§]	**773**	**528**	**435**	**363**	**414**	**343**	**NA**

Abbreviation: NA = not applicable.

* Data from 45 reporting areas; excludes seven reporting areas (California, Connecticut, Illinois, Maryland, New Hampshire, New Jersey, and Wisconsin) that did not report, did not report age among adolescents by individual year, or did not meet reporting standards.

[†] Percentages for the individual component categories might not add to 100% because of rounding.

[§] Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these small values have been suppressed.

[¶] For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

** Data reported from facilities physically situated in state only.

[††] Number of abortions obtained by women in a specific age group per 1,000 women in that same age group. Adolescents aged 13–14 years were used as the denominator for the group of adolescents aged <15 years. For the total abortion rate only, abortions for women of unknown age were distributed according to the distribution of abortions among women of known age.

[§§] Number of abortions obtained by women in a specific age group per 1,000 live births to women in that same age group. For the total abortion ratio only, abortions for women of unknown age were distributed according to the distribution of abortions among women of known age.

Top

TABLE 6. Number and percentage of reported abortions, by known race and ethnicity and reporting area of occurrence — selected reporting areas,* United States, 2022

Area	Non-Hispanic			Hispanic	Total abortions reported by known race and ethnicity
	Black	White	Other[†]		
	No. (%)[§]	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[¶]
Alabama	2,017 (54.0)	907 (24.3)	68 (1.8)	742 (19.9)	**3,734 (98.9)**
Alaska	98 (8.6)	547 (48.0)	467 (41.0)	27 (2.4)	**1,139 (91.3)**
Arizona	1,400 (12.7)	3,699 (33.6)	769 (7.0)	5,127 (46.6)	**10,995 (95.4)**
Delaware	1,104 (45.2)	864 (35.3)	55 (2.2)	422 (17.3)	**2,445 (100.0)**
District of Columbia	2,123 (56.6)	489 (13.0)	436 (11.6)	700 (18.7)	**3,748 (93.2)**
Florida	28,192 (36.3)	21,866 (28.2)	2,845 (3.7)	24,679 (31.8)	**77,582 (93.9)**
Georgia	24,104 (67.6)	6,492 (18.2)	1,687 (4.7)	3,399 (9.5)	**35,682 (91.9)**
Idaho	22 (2.2)	658 (65.7)	40 (4.0)	281 (28.1)	**1,001 (97.5)**
Indiana	3,370 (36.5)	4,188 (45.4)	687 (7.4)	981 (10.6)	**9,226 (96.8)**
Kansas	3,016 (24.7)	4,568 (37.5)	1,152 (9.4)	3,461 (28.4)	**12,197 (99.0)**
Kentucky	928 (36.5)	1,215 (47.8)	133 (5.2)	268 (10.5)	**2,544 (99.8)**
Maine	174 (8.3)	1,775 (84.7)	71 (3.4)	76 (3.6)	**2,096 (94.2)**
Michigan	15,901 (54.2)	10,616 (36.2)	1,525 (5.2)	1,305 (4.4)	**29,347 (97.4)**
Minnesota	2,848 (25.8)	5,198 (47.0)	1,630 (14.7)	1,377 (12.5)	**11,053 (90.8)**
Mississippi	1,767 (77.3)	438 (19.2)	22 (1.0)	59 (2.6)	**2,286 (100.0)**

Area	Non-Hispanic			Hispanic	Total abortions reported by known race and ethnicity
	Black	White	Other†		
	No. (%)§	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)¶
Missouri	34 (40.5)	40 (47.6)	—**	—**	**84 (95.5)**
Montana	30 (1.8)	1,364 (80.1)	169 (9.9)	139 (8.2)	**1,702 (100.0)**
Nevada††	1,908 (18.5)	2,865 (27.8)	799 (7.7)	4,740 (46.0)	**10,312 (86.2)**
New York State	7,007 (31.3)	8,683 (38.8)	1,722 (7.7)	4,991 (22.3)	**22,403 (85.1)**
North Carolina	19,576 (51.3)	9,936 (26.0)	3,100 (8.1)	5,579 (14.6)	**38,191 (95.4)**
North Dakota	119 (16.6)	428 (59.8)	121 (16.9)	48 (6.7)	**716 (95.0)**
Oregon	518 (6.6)	4,272 (54.7)	919 (11.8)	2,101 (26.9)	**7,810 (90.1)**
Rhode Island	202 (15.2)	803 (60.4)	69 (5.2)	255 (19.2)	**1,329 (96.1)**
South Carolina	3,463 (47.6)	2,700 (37.1)	315 (4.3)	795 (10.9)	**7,273 (100.0)**
South Dakota	15 (11.0)	84 (61.8)	26 (19.1)	11 (8.1)	**136 (99.3)**
Tennessee	3,448 (55.3)	2,028 (32.5)	213 (3.4)	548 (8.8)	**6,237 (96.7)**
Texas§§	5,194 (30.0)	4,539 (26.2)	922 (5.3)	6,659 (38.5)	**17,314 (98.9)**
Utah	186 (5.1)	1,939 (52.9)	295 (8.0)	1,248 (34.0)	**3,668 (95.9)**
Vermont	43 (4.0)	943 (88.6)	30 (2.8)	48 (4.5)	**1,064 (96.0)**
Virginia¶¶	5,386 (34.8)	3,445 (22.2)	4,586 (29.6)	2,075 (13.4)	**15,492 (92.6)**
West Virginia	109 (13.1)	692 (83.3)	—**	—**	**831 (100.0)**
Wyoming	6 (1.2)	361 (74.3)	29 (6.0)	90 (18.5)	**486 (90.0)**
Total	**134,308 (39.5)**	**108,642 (31.9)**	**24,932 (7.3)**	**72,241 (21.2)**	**340,123 (94.0)*** **
Abortion rate†††	**24.4**	**5.7**	**9.4**	**11.6**	**NA**
Abortion ratio§§§	**429**	**106**	**182**	**165**	**NA**

* Data from 32 reporting areas; excludes 20 reporting areas (Arkansas, California, Colorado, Connecticut, Hawaii, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Nebraska, New Hampshire, New Jersey, New Mexico, New York City, Ohio, Oklahoma, Pennsylvania, Washington, and Wisconsin) that did not report, did not report by race and ethnicity, or did not meet reporting standards.
† Including Alaska Native, American Indian, Asian (Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or other Asian), Pacific Islander (Native Hawaiian, Guamanian or Chamorro, Samoan, or other Pacific Islander), other races, and multiple races.
§ Percentages for the individual component categories might not add to 100% because of rounding.
¶ Percentage is calculated as the number of abortions reported by known race and ethnicity divided by the sum of abortions reported by known and unknown race and ethnicity. Values ≥99.95% are rounded to 100.0%.
** Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these small values have been suppressed.
†† For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.
§§ Reporting form contains only one question for race and ethnicity; therefore, abortions reported for women of Black, White, and other races (Asian and Native American) are not explicitly identified as non-Hispanic.
¶¶ Data reported from facilities physically situated in state only.
*** Percentage is based on a total of 361,987 abortions reported among the areas that met reporting standards for race and ethnicity.
††† Number of abortions obtained by women in a specific racial and ethnic group per 1,000 women aged 15–44 years in that same racial and ethnic group. For the total abortion rate only, abortions for women of unknown race and ethnicity were distributed according to the distribution of abortions among women of known race and ethnicity.
§§§ Number of abortions obtained by women in a specific racial and ethnic group per 1,000 live births to women in that same racial and ethnic group. For the total abortion ratio only, abortions for women of unknown race and ethnicity were distributed according to the distribution of abortions among women of known race and ethnicity.

Top

TABLE 7. Number and percentage of reported abortions, by known marital status and reporting area of occurrence — selected reporting areas,* United States, 2022

Area	Marital status		Total abortions reported by known marital status
	Married	Unmarried	
	No. (%)†	No. (%)	No. (% of all reported abortions)§
Alabama	389 (10.3)	3,385 (89.7)	**3,774 (99.9)**
Arizona	1,777 (15.4)	9,753 (84.6)	**11,530 (100.0)**
Arkansas	127 (7.9)	1,484 (92.1)	**1,611 (99.4)**
Colorado	2,237 (17.1)	10,858 (82.9)	**13,095 (92.5)**
Delaware	229 (9.4)	2,216 (90.6)	**2,445 (100.0)**
Florida	9,601 (13.6)	60,888 (86.4)	**70,489 (85.4)**
Georgia	3,839 (10.3)	33,503 (89.7)	**37,342 (96.2)**
Idaho	176 (17.3)	844 (82.7)	**1,020 (99.3)**
Illinois¶	4,951 (9.2)	49,018 (90.8)	**53,969 (95.6)**
Indiana	1,268 (13.3)	8,262 (86.7)	**9,530 (100.0)**

Area	Marital status		Total abortions reported by known marital status
	Married	Unmarried	
	No. (%)[†]	No. (%)	No. (% of all reported abortions)[§]
Iowa	567 (14.0)	3,490 (86.0)	**4,057 (99.7)**
Kansas	1,746 (14.6)	10,234 (85.4)	**11,980 (97.3)**
Kentucky	310 (12.2)	2,240 (87.8)	**2,550 (100.0)**
Louisiana	397 (8.8)	4,118 (91.2)	**4,515 (98.8)**
Maine	324 (15.3)	1,800 (84.7)	**2,124 (95.5)**
Michigan	3,396 (11.6)	25,792 (88.4)	**29,188 (96.9)**
Minnesota	1,617 (14.3)	9,697 (85.7)	**11,314 (92.9)**
Mississippi	144 (6.3)	2,141 (93.7)	**2,285 (100.0)**
Missouri	33 (37.5)	55 (62.5)	**88 (100.0)**
Montana	313 (18.9)	1,342 (81.1)	**1,655 (97.2)**
Nebraska	331 (13.5)	2,129 (86.5)	**2,460 (96.6)**
Nevada**	1,516 (14.3)	9,082 (85.7)	**10,598 (88.6)**
North Carolina	4,878 (13.2)	32,012 (86.8)	**36,890 (92.1)**
North Dakota	92 (12.3)	659 (87.7)	**751 (99.6)**
Ohio	2,117 (12.3)	15,075 (87.7)	**17,192 (92.9)**
Oklahoma	321 (14.9)	1,835 (85.1)	**2,156 (99.8)**
Rhode Island	180 (13.4)	1,164 (86.6)	**1,344 (97.2)**
South Carolina	936 (12.9)	6,340 (87.1)	**7,276 (100.0)**
South Dakota	24 (17.5)	113 (82.5)	**137 (100.0)**
Tennessee	733 (11.6)	5,601 (88.4)	**6,334 (98.2)**
Texas	2,452 (14.0)	15,061 (86.0)	**17,513 (100.0)**
Utah	831 (21.8)	2,977 (78.2)	**3,808 (99.6)**
Vermont	193 (18.7)	838 (81.3)	**1,031 (93.1)**
Virginia[††,§§]	1,165 (7.0)	15,557 (93.0)	**16,722 (100.0)**

Area	Marital status		Total abortions reported by known marital status
	Married	Unmarried	
	No. (%)[†]	No. (%)	No. (% of all reported abortions)[§]
West Virginia	144 (17.3)	687 (82.7)	**831 (100.0)**
Wisconsin	337 (10.2)	2,982 (89.8)	**3,319 (99.6)**
Total	**49,691 (12.3)**	**353,232 (87.7)**	**402,923 (94.0)[¶¶]**
Abortion ratio***	**37**	**376**	**NA**

Abbreviation: NA = not applicable.

* Data from 36 reporting areas; excludes 16 reporting areas (Alaska, California, Connecticut, District of Columbia, Hawaii, Maryland, Massachusetts, New Hampshire, New Jersey, New Mexico, New York City, New York State, Oregon, Pennsylvania, Washington, and Wyoming) that did not report, did not report by marital status, or did not meet reporting standards.

[†] Percentages for the individual component categories might not add to 100% because of rounding.

[§] Percentage is calculated as the number of abortions reported by known marital status divided by the sum of abortions reported by known and unknown marital status. Values ≥99.95% are rounded to 100.0%.

[¶] Includes residents only.

** For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

[††] Recorded as patient married or not married to father.

[§§] Data reported from facilities physically situated in state only.

[¶¶] Percentage is based on a total of 428,577 abortions reported among the areas that met reporting standards for marital status; reporting standards for marital status were applied to abortions for residents of Illinois only.

*** Number of abortions obtained by marital status per 1,000 live births to women of the same marital status. For the total abortion ratio only, abortions for women of unknown marital status were distributed according to the distribution of abortions among women of known marital status.

Top

TABLE 8. Number and percentage of reported abortions, by known number of previous live births and reporting area of occurrence — selected reporting areas,* United States, 2022

Area	No. of previous live births					Total abortions reported by known number of previous live births
	0	1	2	3	≥4	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Alabama	1,320 (34.9)	1,052 (27.9)	778 (20.6)	401 (10.6)	226 (6.0)	**3,777 (100.0)**
Alaska	587 (47.1)	263 (21.1)	216 (17.3)	100 (8.0)	81 (6.5)	**1,247 (100.0)**
Arizona	5,432 (47.9)	2,359 (20.8)	1,939 (17.1)	917 (8.1)	695 (6.1)	**11,342 (98.4)**
Arkansas	526 (32.4)	440 (27.1)	341 (21.0)	174 (10.7)	140 (8.6)	**1,621 (100.0)**

Area	No. of previous live births					Total abortions reported by known number of previous live births
	0	1	2	3	≥4	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Colorado	8,302 (59.3)	2,478 (17.7)	1,860 (13.3)	866 (6.2)	488 (3.5)	**13,994 (98.9)**
Delaware	1,025 (41.9)	579 (23.7)	490 (20.0)	207 (8.5)	144 (5.9)	**2,445 (100.0)**
Florida	30,388 (38.1)	20,855 (26.2)	16,485 (20.7)	7,218 (9.1)	4,725 (5.9)	**79,671 (96.5)**
Georgia	15,314 (39.5)	9,444 (24.3)	7,639 (19.7)	3,767 (9.7)	2,648 (6.8)	**38,812 (100.0)**
Hawaii	1,048 (55.0)	314 (16.5)	289 (15.2)	150 (7.9)	103 (5.4)	**1,904 (96.6)**
Idaho	504 (49.4)	222 (21.8)	163 (16.0)	74 (7.3)	57 (5.6)	**1,020 (99.3)**
Indiana	3,642 (38.2)	2,295 (24.1)	1,929 (20.2)	1,007 (10.6)	653 (6.9)	**9,526 (100.0)**
Iowa	1,793 (44.2)	872 (21.5)	735 (18.1)	368 (9.1)	293 (7.2)	**4,061 (99.8)**
Kansas	5,038 (40.9)	2,863 (23.2)	2,397 (19.5)	1,226 (10.0)	793 (6.4)	**12,317 (100.0)**
Kentucky	857 (33.6)	702 (27.5)	559 (21.9)	260 (10.2)	171 (6.7)	**2,549 (100.0)**
Louisiana	1,432 (31.3)	1,203 (26.3)	1,046 (22.9)	524 (11.5)	365 (8.0)	**4,570 (100.0)**
Maine	1,113 (50.4)	465 (21.1)	368 (16.7)	164 (7.4)	97 (4.4)	**2,207 (99.2)**
Massachusetts	7,627 (48.3)	3,648 (23.1)	2,767 (17.5)	1,170 (7.4)	580 (3.7)	**15,792 (88.9)**
Michigan[¶]	10,558 (35.1)	7,627 (25.4)	6,482 (21.5)	3,161 (10.5)	2,256 (7.5)	**30,084 (99.9)**
Minnesota	5,168 (42.5)	2,700 (22.2)	2,293 (18.8)	1,190 (9.8)	821 (6.7)	**12,172 (100.0)**
Mississippi	717 (31.4)	599 (26.2)	518 (22.7)	250 (10.9)	202 (8.8)	**2,286 (100.0)**

Area	No. of previous live births					Total abortions reported by known number of previous live births
	0	1	2	3	≥4	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Missouri	28 (31.8)	19 (21.6)	17 (19.3)	12 (13.6)	12 (13.6)	**88 (100.0)**
Montana	879 (51.6)	383 (22.5)	256 (15.0)	116 (6.8)	68 (4.0)	**1,702 (100.0)**
Nebraska	1,110 (43.7)	532 (21.0)	467 (18.4)	248 (9.8)	182 (7.2)	**2,539 (99.7)**
Nevada**	5,081 (44.0)	2,517 (21.8)	2,136 (18.5)	1,066 (9.2)	758 (6.6)	**11,558 (96.7)**
New Mexico	4,764 (44.1)	2,357 (21.8)	1,906 (17.7)	1,005 (9.3)	760 (7.0)	**10,792 (92.0)**
North Carolina	13,840 (37.7)	8,790 (23.9)	7,269 (19.8)	3,731 (10.2)	3,113 (8.5)	**36,743 (91.8)**
North Dakota	312 (41.4)	163 (21.6)	144 (19.1)	77 (10.2)	58 (7.7)	**754 (100.0)**
Ohio[††]	6,348 (35.3)	4,683 (26.1)	3,795 (21.1)	1,874 (10.4)	1,269 (7.1)	**17,969 (97.1)**
Oregon	4,602 (53.7)	1,705 (19.9)	1,290 (15.1)	593 (6.9)	375 (4.4)	**8,565 (98.8)**
Pennsylvania	13,143 (37.7)	8,913 (25.6)	7,180 (20.6)	3,425 (9.8)	2,177 (6.2)	**34,838 (100.0)**
Rhode Island	646 (47.1)	334 (24.4)	230 (16.8)	111 (8.1)	50 (3.6)	**1,371 (99.1)**
South Carolina	3,137 (43.1)	1,821 (25.0)	1,320 (18.1)	669 (9.2)	329 (4.5)	**7,276 (100.0)**
South Dakota	58 (42.3)	38 (27.7)	16 (11.7)	17 (12.4)	8 (5.8)	**137 (100.0)**
Tennessee	2,183 (33.8)	1,719 (26.7)	1,386 (21.5)	693 (10.7)	469 (7.3)	**6,450 (100.0)**
Texas	7,083 (40.4)	4,054 (23.1)	3,580 (20.4)	1,778 (10.2)	1,019 (5.8)	**17,514 (100.0)**
Utah	2,012 (52.6)	773 (20.2)	576 (15.1)	266 (7.0)	197 (5.2)	**3,824 (100.0)**

Area	No. of previous live births					Total abortions reported by known number of previous live births
	0	1	2	3	≥4	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Vermont	645 (58.2)	212 (19.1)	142 (12.8)	68 (6.1)	41 (3.7)	**1,108 (100.0)**
Virginia[§§]	4,823 (28.8)	4,588 (27.4)	3,373 (20.2)	1,954 (11.7)	1,984 (11.9)	**16,722 (100.0)**
Washington	10,184 (50.6)	4,113 (20.4)	3,438 (17.1)	1,526 (7.6)	860 (4.3)	**20,121 (99.6)**
West Virginia	282 (34.0)	229 (27.6)	185 (22.3)	80 (9.6)	54 (6.5)	**830 (99.9)**
Wyoming	264 (48.9)	113 (20.9)	89 (16.5)	45 (8.3)	29 (5.4)	**540 (100.0)**
Total	**183,815 (40.6)**	**109,036 (24.1)**	**88,089 (19.5)**	**42,548 (9.4)**	**29,350 (6.5)**	**452,838 (97.7)[¶¶]**

* Data from 41 reporting areas; excludes 11 reporting areas (California, Connecticut, District of Columbia, Illinois, Maryland, New Hampshire, New Jersey, New York City, New York State, Oklahoma, and Wisconsin) that did not report, did not report by number of previous live births, or did not meet reporting standards.

[†] Percentages for the individual component categories might not add to 100% because of rounding.

[§] Percentage is calculated as the number of abortions reported by known number of previous live births divided by the sum of abortions reported by known and unknown number of previous live births. Values ≥99.95% are rounded to 100.0%.

[¶] Recorded as the number of previous pregnancies carried to term.

** For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

[††] Recorded as the number of living children.

[§§] Data reported from facilities physically situated in state only.

[¶¶] Percentage is based on a total of 463,579 abortions reported among the areas that met reporting standards for the number of previous live births.

Top

TABLE 9. Number and percentage of reported abortions, by known number of previous induced abortions and reporting area of occurrence — selected reporting areas,* United States, 2022

Area	No. of previous induced abortions				Total abortions reported by known number of previous induced abortions
	0	1	2	≥3	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Alabama	2,339 (61.9)	909 (24.1)	355 (9.4)	174 (4.6)	**3,777 (100.0)**
Alaska	840 (67.4)	277 (22.2)	91 (7.3)	39 (3.1)	**1,247 (100.0)**
Arizona	7,487 (66.3)	2,649 (23.4)	791 (7.0)	373 (3.3)	**11,300 (98.0)**

Area	No. of previous induced abortions				Total abortions reported by known number of previous induced abortions
	0	1	2	≥3	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Arkansas	1,036 (63.9)	334 (20.6)	132 (8.1)	119 (7.3)	**1,621 (100.0)**
Colorado	10,154 (71.9)	2,789 (19.7)	822 (5.8)	359 (2.5)	**14,124 (99.8)**
Delaware	1,595 (65.3)	547 (22.4)	198 (8.1)	101 (4.1)	**2,441 (99.8)**
Florida	36,777 (46.6)	21,328 (27.0)	11,009 (14.0)	9,776 (12.4)	**78,890 (95.5)**
Georgia	24,020 (61.9)	8,627 (22.2)	3,892 (10.0)	2,269 (5.8)	**38,808 (100.0)**
Hawaii	1,156 (60.1)	462 (24.0)	182 (9.5)	122 (6.3)	**1,922 (97.6)**
Idaho	731 (71.2)	208 (20.3)	67 (6.5)	21 (2.0)	**1,027 (100.0)**
Indiana	6,241 (65.5)	2,130 (22.4)	751 (7.9)	405 (4.3)	**9,527 (100.0)**
Iowa	2,814 (69.3)	847 (20.9)	261 (6.4)	138 (3.4)	**4,060 (99.8)**
Kansas	8,481 (68.9)	2,620 (21.3)	810 (6.6)	405 (3.3)	**12,316 (100.0)**
Kentucky	1,610 (63.2)	583 (22.9)	204 (8.0)	151 (5.9)	**2,548 (99.9)**
Louisiana	2,933 (64.2)	1,119 (24.5)	349 (7.6)	169 (3.7)	**4,570 (100.0)**
Maine	1,435 (65.5)	525 (24.0)	173 (7.9)	57 (2.6)	**2,190 (98.4)**
Massachusetts	8,505 (49.9)	4,835 (28.4)	2,054 (12.1)	1,641 (9.6)	**17,035 (95.9)**
Michigan	15,030 (50.0)	7,390 (24.6)	4,229 (14.1)	3,434 (11.4)	**30,083 (99.9)**
Minnesota	7,500 (61.7)	2,731 (22.5)	1,028 (8.5)	894 (7.4)	**12,153 (99.8)**

Area	No. of previous induced abortions				Total abortions reported by known number of previous induced abortions
	0	1	2	≥3	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Mississippi	1,549 (67.8)	494 (21.6)	175 (7.7)	68 (3.0)	**2,286 (100.0)**
Missouri	73 (83.0)	9 (10.2)	—**	—**	**88 (100.0)**
Montana	860 (50.5)	579 (34.0)	184 (10.8)	79 (4.6)	**1,702 (100.0)**
Nebraska	1,840 (72.5)	481 (19.0)	143 (5.6)	74 (2.9)	**2,538 (99.6)**
Nevada[¶]	6,906 (59.6)	2,661 (23.0)	1,160 (10.0)	853 (7.4)	**11,580 (96.8)**
New Mexico	2,141 (18.8)	6,552 (57.6)	2,044 (18.0)	636 (5.6)	**11,373 (96.9)**
North Carolina	23,053 (63.3)	7,815 (21.5)	3,436 (9.4)	2,101 (5.8)	**36,405 (90.9)**
North Dakota	522 (69.2)	147 (19.5)	47 (6.2)	38 (5.0)	**754 (100.0)**
Ohio	10,888 (60.6)	4,000 (22.3)	1,811 (10.1)	1,260 (7.0)	**17,959 (97.1)**
Oregon	5,638 (66.0)	1,765 (20.7)	687 (8.0)	453 (5.3)	**8,543 (98.5)**
Pennsylvania	18,242 (52.4)	8,480 (24.3)	4,111 (11.8)	4,005 (11.5)	**34,838 (100.0)**
Rhode Island	826 (60.0)	319 (23.2)	128 (9.3)	103 (7.5)	**1,376 (99.5)**
South Carolina	4,792 (65.9)	1,617 (22.2)	586 (8.1)	281 (3.9)	**7,276 (100.0)**
South Dakota	98 (71.5)	26 (19.0)	—**	—**	**137 (100.0)**
Tennessee	4,036 (62.6)	1,600 (24.8)	544 (8.4)	268 (4.2)	**6,448 (99.9)**
Texas	10,692 (61.0)	4,416 (25.2)	1,573 (9.0)	833 (4.8)	**17,514 (100.0)**
Utah	2,978 (77.9)	617 (16.1)	172 (4.5)	57 (1.5)	**3,824 (100.0)**
Vermont	732 (66.1)	243 (21.9)	83 (7.5)	50 (4.5)	**1,108 (100.0)**

Area	No. of previous induced abortions				Total abortions reported by known number of previous induced abortions
	0	1	2	≥3	
	No. (%)[†]	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[§]
Virginia[††]	4,823 (28.8)	4,588 (27.4)	3,373 (20.2)	3,938 (23.5)	**16,722 (100.0)**
Washington	12,308 (61.3)	4,551 (22.7)	1,793 (8.9)	1,426 (7.1)	**20,078 (99.4)**
West Virginia	591 (71.2)	153 (18.4)	55 (6.6)	31 (3.7)	**830 (99.9)**
Wyoming	389 (72.0)	109 (20.2)	31 (5.7)	11 (2.0)	**540 (100.0)**
Total	**254,661 (56.1)**	**112,132 (24.7)**	**49,549 (10.9)**	**37,216 (8.2)**	**453,558 (97.8)[§§]**

* Data from 41 reporting areas; excludes 11 reporting areas (California, Connecticut, District of Columbia, Illinois, Maryland, New Hampshire, New Jersey, New York City, New York State, Oklahoma, and Wisconsin) that did not report, did not report by number of previous induced abortions, or did not meet reporting standards.

† Percentages for the individual component categories might not add to 100% because of rounding.

§ Percentage is calculated as the number of abortions reported by known number of previous induced abortions divided by the sum of abortions reported by known and unknown number of previous induced abortions. Values ≥99.95% are rounded to 100.0%.

¶ For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

** Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these small values have been suppressed.

†† Data reported from facilities physically situated in state only.

§§ Percentage is based on a total of 463,579 abortions reported among the areas that met reporting standards for the number of previous induced abortions.

Top

TABLE 10. Number and percentage of reported abortions, by known weeks of gestation* and reporting area of occurrence — selected reporting areas,† United States, 2022

Area	Weeks of gestation							Total abortions reported by known gestational age
	≤6	7–9	10–13	14–15	16–17	18–20	≥21	
	No. (%)[§]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[¶]
Alabama**	848 (22.5)	1,816 (48.1)	731 (19.4)	171 (4.5)	89 (2.4)	97 (2.6)	23 (0.6)	**3,775 (99.9)**
Alaska	417 (33.4)	518 (41.5)	229 (18.4)	39 (3.1)	43 (3.4)	—[††]	—[††]	**1,247 (100.0)**
Arizona	3,444 (29.9)	5,319 (46.2)	1,885 (16.4)	382 (3.3)	188 (1.6)	172 (1.5)	115 (1.0)	**11,505 (99.8)**

Area	Weeks of gestation							Total abortions reported by known gestational age
	≤6	7–9	10–13	14–15	16–17	18–20	≥21	
	No. (%)[§]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[¶]
Arkansas**	20 (1.2)	530 (32.7)	702 (43.3)	155 (9.6)	94 (5.8)	106 (6.5)	14 (0.9)	**1,621 (100.0)**
Colorado	4,915 (34.8)	5,829 (41.2)	1,907 (13.5)	341 (2.4)	344 (2.4)	313 (2.2)	488 (3.5)	**14,137 (99.9)**
Delaware	779 (32.3)	1,100 (45.6)	389 (16.1)	92 (3.8)	12 (0.5)	18 (0.7)	24 (1.0)	**2,414 (98.7)**
Florida	28,983 (35.1)	35,418 (42.9)	13,314 (16.1)	2,693 (3.3)	882 (1.1)	742 (0.9)	549 (0.7)	**82,581 (100.0)**
Georgia	23,286 (60.0)	10,582 (27.3)	3,278 (8.4)	630 (1.6)	426 (1.1)	492 (1.3)	125 (0.3)	**38,819 (100.0)**
Hawaii	649 (33.0)	873 (44.4)	273 (13.9)	72 (3.7)	38 (1.9)	28 (1.4)	33 (1.7)	**1,966 (99.8)**
Idaho	399 (39.9)	414 (41.4)	143 (14.3)	37 (3.7)	—[††]	5 (0.5)	—[††]	**1,000 (97.4)**
Indiana	2,332 (24.5)	5,329 (55.9)	1,765 (18.5)	28 (0.3)	19 (0.2)	28 (0.3)	29 (0.3)	**9,530 (100.0)**
Iowa	1,210 (29.8)	1,895 (46.6)	681 (16.8)	113 (2.8)	88 (2.2)	65 (1.6)	12 (0.3)	**4,064 (99.9)**
Kansas	3,165 (25.7)	5,681 (46.1)	2,381 (19.3)	485 (3.9)	282 (2.3)	273 (2.2)	50 (0.4)	**12,317 (100.0)**
Kentucky	746 (29.3)	1,192 (46.7)	399 (15.6)	95 (3.7)	48 (1.9)	59 (2.3)	11 (0.4)	**2,550 (100.0)**
Louisiana	544 (11.9)	1,760 (38.5)	1,647 (36.0)	418 (9.1)	178 (3.9)	23 (0.5)	0 (0.0)	**4,570 (100.0)**
Maine	715 (32.2)	1,075 (48.4)	325 (14.6)	46 (2.1)	36 (1.6)	—[††]	—[††]	**2,221 (99.8)**
Michigan	10,661 (35.5)	12,122 (40.4)	4,369 (14.6)	1,141 (3.8)	669 (2.2)	659 (2.2)	406 (1.4)	**30,027 (99.7)**
Minnesota	4,438 (36.7)	4,839 (40.0)	1,702 (14.1)	413 (3.4)	276 (2.3)	195 (1.6)	227 (1.9)	**12,090 (99.3)**

Area	Weeks of gestation							Total abortions reported by known gestational age
	≤6	7–9	10–13	14–15	16–17	18–20	≥21	
	No. (%)[§]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[¶]
Mississippi	305 (13.3)	1,327 (58.0)	509 (22.3)	137 (6.0)	7 (0.3)	—[††]	—[††]	**2,286 (100.0)**
Missouri	—[††]	9 (10.2)	—[††]	14 (15.9)	14 (15.9)	24 (27.3)	15 (17.0)	**88 (100.0)**
Montana	877 (52.0)	587 (34.8)	134 (7.9)	52 (3.1)	23 (1.4)	—[††]	—[††]	**1,687 (99.1)**
Nebraska	833 (32.7)	1,031 (40.5)	487 (19.1)	91 (3.6)	61 (2.4)	31 (1.2)	13 (0.5)	**2,547 (100.0)**
Nevada[§§]	4,248 (36.8)	4,755 (41.2)	1,620 (14.1)	343 (3.0)	207 (1.8)	222 (1.9)	133 (1.2)	**11,528 (96.4)**
New Mexico	4,442 (41.9)	3,176 (29.9)	1,526 (14.4)	372 (3.5)	337 (3.2)	322 (3.0)	434 (4.1)	**10,609 (90.4)**
New York City	19,371 (41.8)	17,498 (37.8)	5,383 (11.6)	1,319 (2.8)	815 (1.8)	911 (2.0)	1,054 (2.3)	**46,351 (100.0)**
North Carolina	13,506 (33.8)	17,299 (43.3)	6,246 (15.6)	1,247 (3.1)	906 (2.3)	747 (1.9)	14 (0.0)	**39,965 (99.8)**
North Dakota	274 (36.3)	310 (41.1)	130 (17.2)	32 (4.2)	8 (1.1)	0 (0.0)	0 (0.0)	**754 (100.0)**
Ohio	6,638 (35.9)	7,639 (41.3)	2,653 (14.3)	641 (3.5)	413 (2.2)	408 (2.2)	107 (0.6)	**18,499 (100.0)**
Oklahoma	369 (17.2)	1,011 (47.0)	542 (25.2)	143 (6.7)	58 (2.7)	19 (0.9)	7 (0.3)	**2,149 (99.5)**
Oregon	3,851 (44.5)	3,190 (36.8)	907 (10.5)	199 (2.3)	158 (1.8)	185 (2.1)	171 (2.0)	**8,661 (99.9)**
Rhode Island	559 (40.4)	384 (27.8)	254 (18.4)	82 (5.9)	44 (3.2)	52 (3.8)	8 (0.6)	**1,383 (100.0)**
South Carolina**	1,850 (25.4)	2,732 (37.5)	2,350 (32.3)	305 (4.2)	10 (0.1)	14 (0.2)	15 (0.2)	**7,276 (100.0)**
South Dakota	—[††]	59 (43.1)	—[††]	—[††]	—[††]	0 (0.0)	0 (0.0)	**137 (100.0)**

Area	Weeks of gestation							Total abortions reported by known gestational age
	≤6	7–9	10–13	14–15	16–17	18–20	≥21	
	No. (%)[§]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (% of all reported abortions)[¶]
Tennessee	1,890 (29.3)	2,707 (42.0)	1,422 (22.0)	229 (3.6)	148 (2.3)	47 (0.7)	7 (0.1)	**6,450 (100.0)**
Texas**	17,191 (98.2)	288 (1.6)	7 (0.0)	—[††]	—[††]	12 (0.1)	8 (0.0)	**17,514 (100.0)**
Utah	1,757 (45.9)	1,336 (34.9)	477 (12.5)	100 (2.6)	76 (2.0)	48 (1.3)	30 (0.8)	**3,824 (100.0)**
Vermont	493 (44.7)	399 (36.1)	129 (11.7)	21 (1.9)	23 (2.1)	23 (2.1)	16 (1.4)	**1,104 (99.6)**
Virginia[¶¶]	8,175 (48.9)	5,792 (34.6)	1,856 (11.1)	335 (2.0)	140 (0.8)	198 (1.2)	225 (1.3)	**16,721 (100.0)**
Washington	9,228 (45.8)	7,356 (36.5)	1,992 (9.9)	461 (2.3)	269 (1.3)	319 (1.6)	525 (2.6)	**20,150 (99.8)**
West Virginia	253 (30.5)	374 (45.1)	152 (18.3)	40 (4.8)	9 (1.1)	—[††]	—[††]	**829 (99.8)**
Wyoming	350 (64.9)	181 (33.6)	8 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**539 (99.8)**
Total	**184,042 (40.2)**	**175,732 (38.4)**	**64,961 (14.2)**	**13,518 (3.0)**	**7,444 (1.6)**	**6,892 (1.5)**	**4,896 (1.1)**	**457,485 (99.6)*** **

* Gestational age based on clinician's estimate (Alaska, Arizona, Colorado, Delaware, Georgia, Hawaii, Idaho, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Mexico, New York City, North Carolina, North Dakota, Ohio, Oregon, Rhode Island, South Dakota, Tennessee, Vermont, Washington, West Virginia, and Wyoming); gestational age calculated from the last normal menstrual period (Florida, Oklahoma and Utah); clinician's estimate of gestation based on estimated date of conception (Virginia); and probable postfertilization age (Alabama, Arkansas, South Carolina, and Texas).

† Data from 41 reporting areas; excludes 11 reporting areas (California, Connecticut, District of Columbia, Illinois, Maryland, Massachusetts, New Hampshire, New Jersey, New York State, Pennsylvania, and Wisconsin) that did not report, did not report by gestational age, or did not meet reporting standards.

§ Percentages for the individual component categories might not add to 100% because of rounding.

¶ Percentage is calculated as the number of abortions reported by known gestational age divided by the sum of abortions reported by known and unknown gestational age. Values ≥99.95% are rounded to 100.0%.

** Two weeks were added to the probable postfertilization age to provide a corresponding measure to gestational age based on the clinician's estimate.

†† Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these small values have been suppressed.

§§ For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

¶¶ Data reported from facilities physically situated in state only.

*** Percentage is based on a total of 459,517 abortions reported among the areas that met reporting standards for gestational age.

Top

TABLE 11. Percentage of reported abortions, by known weeks of gestation and year — selected reportin States, 2013–2022

Weeks of gestation	Year									
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2(
≤13 weeks (%)†	**92.0**	**91.3**	**91.3**	**91.3**	**91.6**	**91.8**	**92.3**	**92.7**	**92.9**	
≤6	34.8	33.6	34.2	34.4	35.3	36.5	37.9	39.6	39.4	
7–9	40.2	40.3	40.3	40.7	40.7	40.1	39.9	39.6	39.7	
10–13	17.0	17.3	16.7	16.3	15.5	15.2	14.4	13.5	13.8	
>13 weeks (%)†	**8.0**	**8.7**	**8.7**	**8.7**	**8.4**	**8.2**	**7.7**	**7.3**	**7.1**	
14–15	3.2	3.5	3.4	3.5	3.3	3.3	3.1	3.0	2.9	
16–17	1.8	2.1	2.1	2.1	2.1	2.0	1.8	1.7	1.7	
18–20	1.8	1.9	1.9	1.9	1.9	1.9	1.7	1.6	1.6	
≥21	1.2	1.3	1.3	1.2	1.2	1.1	1.1	1.0	1.0	
Total no.§	**408,958**	**399,156**	**389,411**	**382,097**	**369,992**	**370,647**	**375,636**	**364,626**	**380,753**	**3(**

Abbreviation: NA = not applicable.

* Data from 36 reporting areas; excludes 16 areas (California, Connecticut, District of Columbia, Florida, Illinois, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York State, Pennsylvania, Rhode Island, Tennessee, Wisconsin, and Wyoming) that did not report, did not report by weeks of gestation, or did not meet reporting standards for ≥1 year.

† Percentages for the individual component categories might not add to 100% because of rounding.

§ By year, the total number of abortions represents 72.7%–91.4% of all abortions reported to CDC among the areas that met reporting standards for gestational age during 2013–2022.

Top

TABLE 12. Number and percentage of reported abortions, by known method type and reporting area of selected reporting areas,* United States, 2022

Area	Surgical†			Medication			Intrauterine instillation§	Hyst or hyst
	≤13 weeks' gestation	>13 weeks' gestation	Unknown gestational age	≤9 weeks' gestation	>9 weeks' gestation	Unknown gestational age		
	No. (%)¶	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No.
Alabama††	1,210 (32.1)	369 (9.8)	—§§	1,967 (52.1)	226 (6.0)	—§§	0 (0.0)	
Alaska	561 (45.0)	81 (6.5)	—§§	574 (46.1)	29 (2.3)	0 (0.0)	—§§	
Arizona	4,829 (41.9)	831 (7.2)	8 (0.1)	5,349 (46.4)	494 (4.3)	17 (0.1)	0 (0.0)	
Arkansas††	873 (53.9)	369 (22.8)	0 (0.0)	216 (13.3)	163 (10.1)	0 (0.0)	0 (0.0)	
Colorado	3,198 (24.9)	790 (6.2)	11 (0.1)	8,118 (63.3)	708 (5.5)	6 (0.0)	—§§	
Connecticut¶¶	NA	NA	3,409 (30.7)	NA	NA	7,701 (69.3)	—§§	
Delaware	512 (21.2)	125 (5.2)	16 (0.7)	1,563 (64.8)	184 (7.6)	13 (0.5)	0 (0.0)	
District of Columbia***	1,599 (39.7)	437 (10.9)	0 (0.0)	NA	NA	1,987 (49.4)	0 (0.0)	
Florida	30,101 (37.6)	4,387 (5.5)	—§§	41,469 (51.8)	4,019 (5.0)	0 (0.0)	0 (0.0)	
Georgia	9,778 (25.2)	1,664 (4.3)	—§§	26,369 (67.9)	1,006 (2.6)	—§§	0 (0.0)	
Hawaii	796 (40.8)	165 (8.5)	—§§	934 (47.8)	54 (2.8)	—§§	0 (0.0)	
Idaho	325 (31.6)	41 (4.0)	7 (0.7)	593 (57.7)	41 (4.0)	20 (1.9)	0 (0.0)	
Indiana	4,419 (46.4)	64 (0.7)	0 (0.0)	4,895 (51.4)	152 (1.6)	0 (0.0)	0 (0.0)	
Iowa	808 (19.9)	269 (6.6)	—§§	2,708 (66.6)	278 (6.8)	—§§	0 (0.0)	

Area	Surgical†			Medication			Intrauterine instillation§	Hyst or hyst
	≤13 weeks' gestation	>13 weeks' gestation	Unknown gestational age	≤9 weeks' gestation	>9 weeks' gestation	Unknown gestational age		
	No. (%)¶	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No.
Kansas	3,888 (31.6)	942 (7.6)	0 (0.0)	6,599 (53.6)	888 (7.2)	0 (0.0)	0 (0.0)	(
Kentucky	1,081 (42.4)	212 (8.3)	0 (0.0)	1,253 (49.1)	—§§	0 (0.0)	0 (0.0)	
Louisiana	2,135 (47.0)	617 (13.6)	0 (0.0)	1,635 (36.0)	160 (3.5)	0 (0.0)	0 (0.0)	(
Maine	709 (31.9)	102 (4.6)	—§§	1,275 (57.4)	130 (5.9)	—§§	0 (0.0)	(
Massachusetts†††	NA	NA	8,462 (47.7)	NA	NA	9,276 (52.3)	—§§	
Michigan	11,590 (38.6)	2,783 (9.3)	46 (0.2)	14,489 (48.2)	1,083 (3.6)	34 (0.1)	—§§	
Minnesota	3,652 (30.0)	1,100 (9.0)	29 (0.2)	6,802 (55.9)	534 (4.4)	56 (0.5)	—§§	
Mississippi	238 (10.4)	144 (6.3)	0 (0.0)	1,622 (71.0)	280 (12.3)	0 (0.0)	0 (0.0)	(
Missouri	—§§	46 (54.8)	—§§	0 (0.0)	16 (19.0)	0 (0.0)	0 (0.0)	
Montana	311 (18.3)	88 (5.2)	—§§	1,219 (71.6)	69 (4.1)	11 (0.6)	—§§	(
Nebraska	449 (17.6)	193 (7.6)	0 (0.0)	1,725 (67.8)	178 (7.0)	0 (0.0)	0 (0.0)	(
Nevada§§§	4,596 (41.7)	436 (4.0)	14 (0.1)	5,503 (49.9)	328 (3.0)	143 (1.3)	0 (0.0)	(
New Mexico	3,848 (36.7)	1,071 (10.2)	218 (2.1)	4,522 (43.1)	530 (5.0)	296 (2.8)	—§§	
New York	8,231 (11.5)	1,922 (2.7)	28,821 (40.3)	7,799 (10.9)	1,807 (2.5)	22,856 (31.9)	110 (0.2)	1
New York City	NA	NA	26,988 (58.2)	NA	NA	19,271 (41.6)	98 (0.2)	1

Area	Surgical[†]			Medication			Intrauterine instillation[§]	Hyst or hyst
	≤13 weeks' gestation	>13 weeks' gestation	Unknown gestational age	≤9 weeks' gestation	>9 weeks' gestation	Unknown gestational age		
	No. (%)[¶]	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No.
New York State	8,231 (32.7)	1,922 (7.6)	1,833 (7.3)	7,799 (31.0)	1,807 (7.2)	3,585 (14.2)	12 (0.0)	(
North Carolina	10,040 (25.4)	2,817 (7.1)	39 (0.1)	24,598 (62.3)	1,967 (5.0)	17 (0.0)	—[§§]	
North Dakota	328 (43.5)	31 (4.1)	0 (0.0)	361 (47.9)	34 (4.5)	0 (0.0)	0 (0.0)	(
Ohio	7,801 (42.2)	1,546 (8.4)	—[§§]	9,069 (49.0)	78 (0.4)	0 (0.0)	0 (0.0)	
Oklahoma	515 (24.5)	222 (10.6)	—[§§]	1,171 (55.8)	187 (8.9)	—[§§]	—[§§]	(
Oregon	2,420 (28.2)	657 (7.7)	—[§§]	5,159 (60.2)	305 (3.6)	10 (0.1)	—[§§]	1
Pennsylvania[¶¶]	NA	NA	15,715 (45.3)	NA	NA	19,011 (54.7)	0 (0.0)	(
Rhode Island	934 (67.6)	181 (13.1)	—[§§]	257 (18.6)	8 (0.6)	0 (0.0)	0 (0.0)	
South Carolina[††]	1,718 (23.6)	334 (4.6)	0 (0.0)	3,835 (52.7)	1,382 (19.0)	0 (0.0)	7 (0.1)	(
South Dakota	85 (62.0)	—[§§]	—[§§]	43 (31.4)	—[§§]	0 (0.0)	0 (0.0)	(
Tennessee	2,352 (36.5)	423 (6.6)	—[§§]	3,267 (50.7)	401 (6.2)	0 (0.0)	0 (0.0)	
Texas[††]	5,598 (32.0)	—[§§]	0 (0.0)	11,887 (67.9)	25 (0.1)	0 (0.0)	0 (0.0)	
Utah	1,282 (33.6)	220 (5.8)	—[§§]	2,216 (58.0)	92 (2.4)	0 (0.0)	7 (0.2)	
Vermont	266 (24.1)	78 (7.1)	—[§§]	705 (63.9)	51 (4.6)	—[§§]	0 (0.0)	(
Virginia[¶¶¶]	6,217 (37.3)	875 (5.3)	0 (0.0)	9,205 (55.2)	361 (2.2)	—[§§]	0 (0.0)	

Area	Surgical†			Medication			Intrauterine instillation§	Hyst or hyst
	≤13 weeks' gestation	>13 weeks' gestation	Unknown gestational age	≤9 weeks' gestation	>9 weeks' gestation	Unknown gestational age		
	No. (%)¶	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No.
Washington	5,792 (29.1)	1,515 (7.6)	—§§	12,082 (60.7)	458 (2.3)	37 (0.2)	—§§	(
West Virginia	378 (45.5)	49 (5.9)	—§§	366 (44.1)	35 (4.2)	—§§	0 (0.0)	(
Wisconsin¶¶,****	NA	NA	2,100 (64.0)	NA	NA	1,179 (36.0)	0 (0.0)	(
Wyoming	—§§	0 (0.0)	0 (0.0)	531 (98.3)	8 (1.5)	—§§	0 (0.0)	(
Total	**194,835 (35.5)**	**37,766 (6.9)**	—††††	**291,980 (53.3)**	**23,412 (4.3)**	—§§§§	**138 (0.0)**	**6**

Abbreviation: NA = not applicable.

* Data from 47 reporting areas; excludes five reporting areas (California, Illinois, Maryland, New Hampshire, and New Jersey) that did not report, did not report by method type, or did not meet reporting standards. Areas reporting by method type with unknown gestational age or gestational age reported was not compatible with categorizations presented in this table are included.

† Includes uterine aspiration (might also be called dilation and curettage, aspiration curettage, suction curettage, manual vacuum aspiration, menstrual extraction, or sharp curettage) and dilation and evacuation procedures.

§ Intrauterine instillation reported at ≤12 weeks' gestation is considered as unknown for method type.

¶ Percentages for the individual component categories might not add to 100% because of rounding.

** Percentage is calculated as the number of abortions reported by known method type divided by the sum of abortions reported by known and unknown method type. Values ≥99.95% are rounded to 100.0%.

†† Two weeks were added to the probable postfertilization age to provide a corresponding measure to gestational age based on the clinician's estimate.

§§ Cells with a numerical value in the range of 1–4 and cells that would allow for calculation of these small values have been suppressed.

¶¶ Numbers for surgical abortions ≤13 weeks' and >13 weeks' gestation and medication abortions ≤9 weeks' versus >9 weeks' gestation are not presented because gestational age reported was not compatible with these categorizations.

*** Gestational age is based on clinician's estimate. Numbers for medication abortions at ≤9 weeks versus >9 weeks are not presented because gestational age reported was not compatible with these categorizations.

††† Numbers for surgical abortions at ≤13 weeks' versus >13 weeks' gestation and for medication abortions at ≤9 weeks' versus >9 weeks' gestation are not presented because gestational age data were not provided by method type.

§§§ For August–December 2022, variable was collected for residents only and reported as unknown for nonresidents.

¶¶¶ Data reported from facilities physically situated in state only.

**** Includes residents only. Wisconsin reports as surgical, unspecified and does not differentiate surgical abortions from hysterectomy or hysterotomy. All abortions were reported as surgical or chemically induced. For this report, all surgical abortions were classified as surgical and all chemical abortions as medication.

†††† For the total only, surgical abortions reported without a gestational age were distributed among the surgical abortion

categories according to the distribution of surgical abortions at known gestational age.

§§§§ For the total only, medication abortions reported without a gestational age were distributed among the medication abortion categories according to the distribution of medication abortions at known gestational age.

¶¶¶¶ Percentage is based on a total of 556,872 abortions reported among the areas that met reporting standards for method type.

Top

TABLE 13. Number and percentage of reported abortions, by known weeks of gestation and method type — selected reporting areas,* United States, 2022

	Weeks of gestation							
	≤6	7–9	10–13	14–15	16–17	18–20	≥21	Total
Method type	**No. (%)†**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Surgical§								
≤13 weeks' gestation	41,971 (25.2)	57,516 (34.4)	45,997 (72.4)	NA	NA	NA	NA	**145,484 (34.1)**
>13 weeks' gestation	NA	NA	NA	12,446 (98.1)	6,900 (97.7)	5,902 (94.9)	2,952 (80.0)	**28,200 (6.6)**
Medication¶								
≤9 weeks' gestation	124,263 (74.7)	109,687 (65.6)	NA	NA	NA	NA	NA	**233,950 (54.8)**
>9 weeks' gestation	NA	NA	17,548 (27.6)	237 (1.9)	159 (2.3)	299 (4.8)	717 (19.4)	**18,960 (4.4)**
Intrauterine instillation	—**	—**	0 (0.0)	1 (0.0)	3 (0.0)	9 (0.1)	16 (0.4)	**29 (0.0)**
Hysterectomy or hysterotomy	16 (0.0)	15 (0.0)	4 (0.0)	1 (0.0)	1 (0.0)	8 (0.1)	3 (0.1)	**48 (0.0)**
Total	**166,250 (100.0)**	**167,218 (100.0)**	**63,549 (100.0)**	**12,685 (100.0)**	**7,063 (100.0)**	**6,218 (100.0)**	**3,688 (100.0)**	**426,671 (100.0)**

Abbreviation: NA = not applicable.

* Data from 40 reporting areas; excludes 12 reporting areas (California, Connecticut, District of Columbia, Illinois, Maryland, Massachusetts, New Hampshire, New Jersey, New York City, New York State, Pennsylvania, and Wisconsin) that did not report, did not report by weeks of gestation, did not meet reporting standards, or did not have medication abortion as a specific category on their reporting form.

† For each gestational age category, percentages of all method types might not add to 100% because of rounding.

§ Includes uterine aspiration (might also be called dilation and curettage, aspiration curettage, suction curettage, manual vacuum aspiration, menstrual extraction, or sharp curettage) and dilation and evacuation procedures.

¶ The administration of medication or medications to induce an abortion; at ≤9 weeks' gestation, typically involves the use of mifepristone and misoprostol and at >9 weeks' gestation, typically involves the use of vaginal prostaglandins.

** Intrauterine instillations reported at ≤12 weeks' gestation have not been included with known values.

Top

TABLE 14. Number and percentage of reported abortions, by known weeks of gestation, age group, and race and ethnicity — selected reporting areas, United States, 2022

Characteristic	Weeks of gestation							Total
	≤6	7–9	10–13	14–15	16–17	18–20	≥21	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Age group, yrs*,†								
<15	191 (21.5)	309 (34.8)	226 (25.5)	60 (6.8)	34 (3.8)	39 (4.4)	29 (3.3)	**888 (100.0)**
15–19	11,452 (33.7)	13,174 (38.8)	6,019 (17.7)	1,324 (3.9)	784 (2.3)	694 (2.0)	492 (1.4)	**33,939 (100.0)**
20–24	45,505 (38.6)	46,113 (39.1)	18,079 (15.3)	3,619 (3.1)	1,945 (1.6)	1,668 (1.4)	979 (0.8)	**117,908 (100.0)**
25–29	47,138 (40.8)	45,201 (39.1)	16,039 (13.9)	3,150 (2.7)	1,644 (1.4)	1,497 (1.3)	937 (0.8)	**115,606 (100.0)**
30–34	34,775 (41.7)	31,674 (38.0)	11,474 (13.8)	2,321 (2.8)	1,210 (1.5)	1,122 (1.3)	786 (0.9)	**83,362 (100.0)**
35–39	18,385 (42.4)	16,110 (37.2)	5,784 (13.3)	1,250 (2.9)	707 (1.6)	676 (1.6)	447 (1.0)	**43,359 (100.0)**
≥40	6,695 (46.0)	5,043 (34.7)	1,711 (11.8)	422 (2.9)	270 (1.9)	252 (1.7)	154 (1.1)	**14,547 (100.0)**
Total	**164,141 (40.1)**	**157,624 (38.5)**	**59,332 (14.5)**	**12,146 (3.0)**	**6,594 (1.6)**	**5,948 (1.5)**	**3,824 (0.9)**	**409,609 (100.0)**
Race and ethnicity*,§								
Non-Hispanic								
Black	47,820 (38.2)	48,681 (38.9)	20,098 (16.1)	4,060 (3.2)	1,942 (1.6)	1,718 (1.4)	730 (0.6)	**125,049 (100.0)**
White	41,789 (42.1)	38,105 (38.4)	13,338 (13.4)	2,615 (2.6)	1,419 (1.4)	1,314 (1.3)	723 (0.7)	**99,303 (100.0)**
Other¶	9,668 (42.5)	8,394 (36.9)	3,063 (13.5)	651 (2.9)	353 (1.6)	370 (1.6)	248 (1.1)	**22,747 (100.0)**
Hispanic	28,837 (43.4)	25,529 (38.4)	8,592 (12.9)	1,603 (2.4)	789 (1.2)	764 (1.1)	379 (0.6)	**66,493 (100.0)**
Total	**128,114 (40.9)**	**120,709 (38.5)**	**45,091 (14.4)**	**8,929 (2.8)**	**4,503 (1.4)**	**4,166 (1.3)**	**2,080 (0.7)**	**313,592 (100.0)**

* Percentages for the individual component categories might not add to 100% because of rounding.
† Data from 40 reporting areas; excludes 12 reporting areas (California, Connecticut, District of Columbia, Illinois, Maryland, Massachusetts, New Hampshire, New Jersey, New York City, New York State, Pennsylvania, and Wisconsin) that did not report, did not report weeks of gestation by age, or did not meet reporting standards.
§ Data from 30 reporting areas; excludes 22 reporting areas (Arkansas, California, Colorado, Connecticut, District of Columbia, Hawaii, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Nebraska, New Hampshire, New Jersey, New Mexico, New York City, New York State, Ohio, Oklahoma, Pennsylvania, Washington, and Wisconsin) that did not report, did not report weeks of gestation by race and ethnicity, or did not meet reporting standards.
¶ Including Alaska Native, American Indian, Asian (Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or other Asian), Native Hawaiian or other Pacific Islander (Native Hawaiian, Guamanian or Chamorro, Samoan, or other Pacific Islander), other races, and multiple races.

Top

TABLE 15. Number of deaths and case-fatality rates* for abortion-related deaths reported to CDC, by type of abortion — United States, 1973–2021†

	Type of abortion				
	Induced				
Year	Legal§	Illegal	Unknown¶	Total deaths	CFR per 100,000 legal abortions
1973–1977					**2.09**
1973	25	19	3	**47**	
1974	26	6	1	**33**	
1975	29	4	1	**34**	
1976	11	2	1	**14**	
1977	17	4	0	**21**	
1978–1982					**0.78**
1978	9	7	0	**16**	
1979	22	0	0	**22**	
1980	9	1	2	**12**	
1981	8	1	0	**9**	
1982	11	1	0	**12**	

Year	Type of abortion			Total deaths	CFR per 100,000 legal abortions
	Induced				
	Legal[§]	Illegal	Unknown[¶]		
1983–1987					**0.66**
1983	11	1	0	**12**	
1984	12	0	0	**12**	
1985	11	1	1	**13**	
1986	11	0	2	**13**	
1987	7	2	0	**9**	
1988–1992					**0.74**
1988	16	0	0	**16**	
1989	12	1	0	**13**	
1990	9	0	0	**9**	
1991	11	1	0	**12**	
1992	10	0	0	**10**	
1993–1997					**0.52**
1993	6	1	2	**9**	
1994	10	2	0	**12**	
1995	4	0	0	**4**	
1996	9	0	0	**9**	
1997	7	0	0	**7**	
1998–2002					**0.63**
1998	9	0	0	**9**	
1999	4	0	0	**4**	
2000	11	0	0	**11**	
2001	7	1	0	**8**	
2002	10	0	0	**10**	

Year	Type of abortion			Total deaths	CFR per 100,000 legal abortions
	Induced				
	Legal[§]	Illegal	Unknown[¶]		
2003–2007					**0.60**
2003	10	0	0	**10**	
2004	7	1	0	**8**	
2005	7	0	0	**7**	
2006	7	0	0	**7**	
2007	6	0	0	**6**	
2008–2012					**0.65**
2008	12	0	0	**12**	
2009	8	0	0	**8**	
2010	10	0	0	**10**	
2011	2	0	0	**2**	
2012	4	0	0	**4**	
2013–2021					**0.46**
2013	4	0	0	**4**	
2014	6	0	0	**6**	
2015	2	0	1	**3**	
2016	6	1	1	**8**	
2017	3	0	0	**3**	
2018	2	0	0	**2**	
2019	4	0	0	**4**	
2020	6	0	0	**6**	
2021	5	0	0	**5**	

Abbreviation: CFR = case-fatality rate.

* Number of legal induced abortion–related deaths per 100,000 reported legal induced abortions. Because a substantial number of legal induced abortions occurred outside reporting areas that provided data to CDC, national CFRs (i.e., number of legal induced abortion–related deaths per 100,000 reported legal induced abortions in the United States) were calculated with denominator data from the Guttmacher Institute's national survey of abortion-providing facilities; for 2021,

denominator data for 2020 were used, the most recent year for which data are available. CFRs were computed for consecutive 5-year periods during 1973–2012 and then for a consecutive 9-year period during 2013–2021 because rates based on <20 cases might be unstable.

[†] Certain numbers might differ from those in reports published previously because additional information has been supplied to CDC after publication.

[§] An abortion is defined as legal if it was performed by a licensed clinician within the limits of state or jurisdiction law.

[¶] Unknown whether abortion was induced or spontaneous.

Top

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ATTACHMENT FOUR

United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex



GAO-08-751

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

GAO Accountability • Integrity • Reliability

Highlights

Highlights of GAO-08-751, a report to congressional requesters

Why GAO Did This Study

In September 2000, the Food and Drug Administration (FDA), part of the Department of Health and Human Services (HHS), approved the drug Mifeprex for use in terminating early term pregnancy. FDA approved the drug under a provision of its Subpart H regulations, allowing it to restrict the drug's distribution to assure its safe use. Critics have questioned aspects of the Mifeprex approval process, including the reliance on historically-controlled clinical trials that compare a drug's effects on a condition to the known course of the condition rather than to another drug or placebo. Critics argued that Mifeprex does not fit within the scope of Subpart H, which applies to drugs that treat serious or life-threatening illnesses. Concerns have also been raised about FDA's oversight of the drug since approval, including the agency's response to deaths in U.S. women who had taken the drug.

In this report GAO (1) describes FDA's approval of Mifeprex, including the evidence considered and the restrictions placed on its distribution; (2) compares the Mifeprex approval process to the approval processes for other Subpart H restricted drugs; and (3) compares FDA's postmarket oversight of Mifeprex to its oversight of other Subpart H restricted drugs. GAO reviewed FDA regulations, policies, and records pertaining to its approval and oversight of Mifeprex and the eight other Subpart H restricted drugs. In addition, GAO interviewed FDA officials and external stakeholders.

To view the full product, including the scope and methodology, click on GAO-08-751. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA approved Mifeprex after evaluating the sponsor's initial and revised new drug application through three review cycles. In the first cycle, FDA concluded that the available data supported the safety and efficacy of Mifeprex and that, because the course of pregnancy was well-documented and the effects of the drug were self-evident, the use of historical controls was consistent with FDA regulations. FDA also concluded that before the drug could be approved, the sponsor needed to provide final data from an ongoing U.S. trial, and more detail on restricting the drug's distribution. In the second cycle, FDA concluded that while the U.S. trial data confirmed the drug's safety and efficacy, the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In the final review, FDA concluded that termination of unwanted pregnancy is a serious condition and imposing restrictions under Subpart H was necessary. FDA approved Mifeprex, but required that the sponsor commit to conduct two postmarketing studies, imposed several distribution restrictions intended to ensure that only qualified physicians prescribe the drug, and required that patients attest to understanding the treatment's potential complications.

The approval process for Mifeprex was consistent with the processes for the other Subpart H restricted drugs, although the details of FDA's approval depended on the unique risks and benefits of each drug. Common elements of the approval processes included that FDA needed to evaluate potential limitations in key clinical data (Mifeprex and six of the other drugs), did not approve the drugs in the first review cycle (Mifeprex and five others), and imposed similar types of distribution restrictions on Mifeprex and the other drugs, though the specific details of the restrictions varied across the drugs.

FDA's postmarket oversight of Mifeprex has been consistent with its oversight of other Subpart H restricted drugs. To oversee compliance with distribution restrictions, FDA has reviewed data from all sponsors and conducted inspections for Mifeprex and two other drugs. To oversee compliance with postmarketing study commitments, FDA has relied on required updates from sponsors and found unfulfilled commitments for most drugs, including Mifeprex. To oversee compliance with adverse event reporting requirements, FDA has evaluated data in sponsors' reports and, for Mifeprex and seven other drugs, has conducted inspections that revealed deficiencies for most of these drugs, including Mifeprex. Lastly, FDA has taken similar steps to oversee postmarket safety across the drugs, such as analyzing adverse events. For Mifeprex, FDA investigated the deaths of six U.S. women who developed a severe infection after taking the drug and concluded that the evidence did not establish a causal relationship between Mifeprex and the infections. Finally, FDA has taken similar actions to address emerging safety concerns across the drugs, such as changing labeling.

HHS reviewed a draft of this report and informed GAO that it did not have comments.

Contents

Letter 1

Results in Brief 5
Background 8
FDA Approved Mifeprex under the Subpart H Restricted Distribution Provision After Concluding That Clinical Evidence Supported Its Safety and Efficacy 14
Approval Process for Mifeprex Was Generally Consistent with That of the Other Eight Subpart H Restricted Drugs 25
FDA's Postmarket Oversight of Mifeprex Has Been Consistent with the Agency's Oversight of the Other Subpart H Restricted Drugs 30
Agency Comments 43

Appendix I **Select Drugs Approved by FDA with Restricted Distribution** 44

Appendix II **Detailed Description of Distribution Restrictions for Mifeprex** 45

Appendix III **Prescriber's Agreement for Mifeprex Distribution** 47

Appendix IV **GAO Contact and Staff Acknowledgments** 50

Tables

Table 1: Timeline of Key Events in FDA's Approval of Mifeprex 15
Table 2: Selected Features of Restricted Distribution Programs Imposed by FDA at Time of Approval under Subpart H 28
Table 3: Selected Features of FDA's Oversight of Postmarket Safety for Drugs Approved under Subpart H, as of May 2008 31

Abbreviations

AERS	Adverse Event Reporting System
CDC	Centers for Disease Control and Prevention
ENL	erythema nodosum leprosum
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus / acquired immune deficiency syndrome
NDA	new drug application
REMS	risk evaluation and mitigation strategy
SGE	special government employee

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GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

August 7, 2008

The Honorable Michael B. Enzi
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Jim DeMint
United States Senate

The Honorable Roscoe G. Bartlett
House of Representatives

In September 2000, the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) granted marketing approval to the prescription drug Mifeprex (mifepristone) for the medical termination of early term pregnancy.[1] It remains the only drug approved in the United States for this purpose. FDA approved the drug under a provision of the agency's Subpart H regulations that allows FDA to restrict the distribution or use of a drug in order to assure its safe use.[2] Under this provision FDA can require, as it did for Mifeprex, that distribution be restricted to certain health care providers with specific training or experience. Since the drug's approval, more than 900,000 women are estimated to have taken Mifeprex in the United States.

[1]Mifeprex is the trade name for the mifepristone product marketed in the United States. Mifepristone is the name of the underlying drug substance. Mifepristone is also sometimes called "RU-486," a reference to the name the drug had during laboratory testing.

[2]Subpart H of FDA's drug approval regulations—titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses"—applies to drugs that are intended to treat serious or life-threatening illnesses and provide a meaningful therapeutic benefit to patients over existing treatments. The regulations contain two approval provisions. One provides a process through which FDA may restrict the distribution or use of a drug to assure its safe use. The other provides FDA with flexibilities that allow the agency to accelerate the approval process for certain drugs on the basis of clinical trial endpoints that are considered reasonably likely to predict clinical benefit. See 21 C.F.R. §§ 314.500-560 (2007).

Before a drug can be marketed in the United States, the drug sponsor must submit a new drug application (NDA) to FDA containing data demonstrating the safety and efficacy of the drug.[3] FDA reviews the NDA to determine whether the drug's benefits outweigh its risks.[4] Once FDA completes its review, the agency issues an action letter in which it either approves the drug as safe and effective for its intended use (approval letter), informs the sponsor that the drug is likely to be approved once the deficiencies FDA has identified are resolved (approvable letter), or indicates that approval cannot be obtained without substantial additional information (not approvable letter).[5] If FDA issues an approvable or not approvable letter, a subsequent review cycle can begin once the sponsor has addressed the issues FDA identified. FDA may require, as a condition of approval, that a sponsor agree to restrict the drug's distribution under the agency's Subpart H regulations.[6]

Critics have raised concerns and questions regarding several aspects of FDA's approval process for Mifeprex. For example, questions have been raised about the reliance on data from historically controlled clinical trials—trials that compare a drug's effects on a condition within the study population to the known course of that same condition in patients or

[3]A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

[4]FDA also reviews supplemental NDAs, which sponsors submit to support proposed changes to a drug's label, a new dosage or strength of the drug, a new patient population or intended use, or changes to the way the drug is manufactured after a drug has an approved NDA.

[5]FDA issued a final rule on July 10, 2008, amending its drug approval regulations. The final rule, among other things, discontinues FDA's use of approvable letters and not approvable letters. Instead, in the event that FDA determines it will not approve an application in its current form, the agency will send applicants a "complete response letter" to indicate that the review cycle for an application is complete and to describe the specific deficiencies the agency identified in the application. The amended regulations are effective on August 11, 2008. See 73 Fed. Reg. 39588-89 (July 10, 2008).

[6]21 C.F.R. § 314.520 (2007). From 1992—the year that the regulations were promulgated—through February 2007, nine drugs, including Mifeprex, had either an NDA or supplemental NDA approved under this restricted distribution provision. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may determine that a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks. The REMS provisions of FDAAA went into effect on March 25, 2008. As part of a REMS, FDA can require "elements to assure safe use," which include restrictions similar to those that can be required under Subpart H regulations. 21 U.S.C. § 355-1(a), (e), (f); Pub. L. No. 110-85, §§ 901, 909(a), 121 Stat. 823, 922, 926-38, 950.

populations that were not part of the trial—to support the safety and efficacy of Mifeprex.[7] FDA regulations allow for the use of such historical controls when the course of the condition in question is well-documented within a comparable population and the effect of the drug is apparent. Questions have also been raised about whether Mifeprex fit within the scope of Subpart H regulations, which apply to drugs that are intended to treat a serious or life-threatening illness. Critics have argued that unwanted pregnancy should not be considered a serious or life-threatening illness. They have also questioned whether FDA's use of Subpart H regulations was consistent with its use of the regulations to approve other drugs.

Additionally, concerns have been raised about FDA's postmarket oversight of Mifeprex, including its efforts to ensure the sponsor's compliance with conditions of approval as well as the actions the agency has taken in response to reported adverse events.[8] For approved drugs, FDA oversees sponsors' compliance with applicable reporting requirements, distribution restrictions, and other conditions of approval.[9] FDA also monitors the drugs' postmarket safety and efficacy. In the case of Mifeprex, six U.S. women have died from severe bacterial infection after taking the drug, raising questions about its safety. Some have questioned FDA's conclusion—which it discussed at a May 2006 congressional hearing—that the available evidence had not established a causal relationship between Mifeprex and the infections.

You asked us to review FDA's approval of Mifeprex and its oversight of the drug since approval. In this report we (1) examine FDA's approach to approving Mifeprex, including the types of evidence considered and the

[7]21 C.F.R. § 314.126(b)(2)(v) (2007). In contrast, clinical trials that use concurrent controls demonstrate the safety and efficacy of a drug by comparing its effects on patients in a treatment group to the effects of a different treatment—such as another drug or a placebo—on patients in a control group within the same study population.

[8]The term postmarket refers to activities occurring after a drug has been approved for marketing. FDA uses the term adverse drug event to refer to any untoward medical event associated with the use of a drug in humans.

[9]FDA regulations require sponsors of approved drugs to submit various postmarket safety reports. See 21 C.F.R. §§ 314.80, 314.81 (2007). Additionally, sponsors of approved drugs must report to FDA annually on the progress of any postmarket studies required by FDA or agreed to by the sponsor. 21 U.S.C. § 356b; 21 C.F.R. § 314.81(b)(2)(vii) (2007). FDA uses such postmarket studies to gather additional information about a drug's safety, efficacy, or use once it is marketed.

restrictions placed on its distribution and use; (2) compare the approval process for Mifeprex to the approval processes for other drugs approved under the restricted distribution provision of Subpart H; and (3) compare FDA's oversight of the use of Mifeprex since its approval to the agency's oversight of the other drugs approved under the restricted distribution provision of Subpart H.

To examine FDA's approval of Mifeprex, we reviewed relevant laws, regulations, policies, and guidance. We reviewed FDA records including an archive of documents pertaining to the approval of Mifeprex.[10] We also reviewed documentation from an FDA advisory committee meeting,[11] testimony statements and the related transcript, FDA responses to congressional requests, an August 2002 citizen's petition and responses from outside organizations, and other documentation pertaining to FDA's approval of Mifeprex. We interviewed FDA officials and external stakeholders who had access to technical information or had conducted analyses pertaining to Mifeprex that were not available through FDA. These included a representative of the sponsor of the Mifeprex application and its licensee,[12] the American College of Obstetricians and Gynecologists and the American Association of Pro Life Obstetricians and Gynecologists.

To compare the approval process for Mifeprex to those of other drugs, we reviewed FDA documentation pertaining to FDA's approval of the other eight drugs that the agency had approved under the restricted distribution

[10]In response to a Freedom of Information Act request, FDA posted certain documents pertaining to its approval of Mifeprex on the agency's Web site (see http://www.fda.gov/cder/archives/mifepristone/default.htm). The documents, which total over 9,000 pages, include a range of sometimes redacted material such as handwritten notes or email communications, communications between the drug sponsor and FDA, meeting minutes, copies of international labeling, and study protocols.

[11]FDA may convene an advisory committee to obtain advice from scientific experts and representatives of the public regarding a drug. FDA requests advice from advisory committees on a variety of matters, including aspects of drug applications and postmarket safety concerns for drug products. The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making. Although the committees provide recommendations to the agency, final decisions are made by FDA.

[12]The Population Council, a non-profit organization involved in reproductive health and population issues, sponsored the Mifeprex application. During the NDA review process, the Population Council contracted with Danco Laboratories, L.L.C. to serve as its licensee with responsibility for commercial manufacturing and marketing of the drug. Following the drug's approval, the Population Council transferred ownership of the Mifeprex NDA to Danco.

provision of Subpart H as of February 2007.[13] Specifically, we examined key documents related to FDA's internal review and approval processes as well as documentation from advisory committee meetings in order to identify commonalities and differences in FDA's process across the nine Subpart H restricted drugs, including Mifeprex. In our examination we focused on issues that had arisen during FDA's review of Mifeprex to determine whether similar issues had arisen in FDA's review of the other drugs, and how FDA had addressed those issues for the other drugs.

To compare FDA's oversight of the use of Mifeprex since approval to the agency's oversight of the other Subpart H restricted drugs, we reviewed relevant regulations and FDA guidance. We also examined FDA documentation on the agency's oversight of sponsors' compliance with distribution restrictions, postmarketing study commitments, and adverse event reporting requirements for the nine Subpart H restricted drugs. In addition, we reviewed FDA's process for evaluating and responding to postmarket data on adverse events for each drug. Lastly, we interviewed FDA officials and staff who are responsible for postmarket oversight of these drugs. We conducted our work from February 2007 through August 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Results in Brief

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of its Subpart H regulations after examining the NDA through three review cycles. In its first review, FDA concluded that the available evidence supported the safety and efficacy of Mifeprex. This conclusion was based in part on FDA's determination that because the course of pregnancy was well-documented and the effects of the treatment were self-evident, the reliance on historical controls in three key clinical trials—two conducted in France and one ongoing in the United States—was appropriate and consistent with FDA regulations. FDA issued an approvable letter in September 1996 concluding that the sponsor needed

[13]We initiated our work in February 2007. In June 2007, FDA approved one additional drug—Letairis—under the restricted distribution provision of Subpart H. This drug was not included in our review.

to provide additional information, such as the final data from the U.S. trial and a detailed plan to restrict the drug's distribution, before an approval decision could be made. The second review cycle began when the sponsor submitted a complete response to this letter. FDA issued a second approvable letter in February 2000 after concluding that the new data confirmed the safety and efficacy of Mifeprex for the U.S. market but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In its final review, FDA deliberated about the distribution restrictions and conditions of use needed to assure the safe use of the drug. FDA concluded that termination of an unwanted pregnancy is a serious condition and that the drug can allow patients to avoid a surgical procedure and therefore Mifeprex fit within the scope of Subpart H. FDA further concluded that the drug could only be used safely if distribution was limited to qualified physicians. The sponsor argued that the drug did not treat a serious condition and that because they had voluntarily agreed to the restrictions FDA had requested, it was neither appropriate nor necessary to impose the restrictions under Subpart H. However, the sponsor eventually acquiesced to FDA's requirement that approval be under Subpart H. After FDA concluded that the sponsor had adequately revised its distribution plan and addressed the remaining issues identified in FDA's reviews, it approved the Mifeprex NDA under Subpart H with several restrictions. These included requiring that prescribing physicians attest to possessing specific skills, agree to fully discuss the treatment with patients, and agree to report certain adverse events to the sponsor; that the drug be distributed directly to physicians by an authorized distributor; and that patients attest to fully understanding the treatment and its potential complications. The drug was also approved subject to the sponsor's commitment to conduct two postmarket studies related to patient outcomes.

The approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs, but the details of FDA's approval process for each drug depended on the drug's unique risks and benefits. One common element across the approval processes for seven of the drugs, including Mifeprex, was that FDA needed to evaluate potential limitations—such as lack of concurrent controls or small sample sizes—in key clinical trials supporting the NDA. For some of these drugs other than Mifeprex, FDA concluded that there were weaknesses in the data submitted in the NDA that needed to be addressed. Another common element for six of the drugs, including Mifeprex, was that FDA issued at least one prior action letter before ultimately approving the drug for marketing under Subpart H. Additionally, the types of distribution restrictions that FDA imposed on Mifeprex were similar to

those the agency imposed on the other drugs, though the details of the restrictions varied depending on the drug. Lastly, eight of the drugs, including Mifeprex, were approved with two or more postmarketing study commitments, each with one or more commitments related to adverse events or patient outcomes of interest.

FDA's postmarket oversight of Mifeprex has been consistent with the agency's postmarket oversight of the other Subpart H restricted drugs. To oversee the drug sponsors' compliance with distribution restrictions, FDA has relied on data submitted by sponsors for all of the drugs. For three of the drugs, one of them Mifeprex, FDA has also completed inspections of the sponsor or its distributors. To oversee compliance with postmarketing study commitments, FDA has relied on updates in required reports from sponsors. Most of the drugs, including Mifeprex, have at least one study commitment that remains unfulfilled. To oversee compliance with adverse event reporting requirements, FDA has relied on sponsors' reports for all of the drugs and has also conducted inspections of the sponsor or its manufacturers for eight of them. FDA has cited the sponsors of seven of the drugs, including Mifeprex, for adverse event reporting deficiencies. To oversee the postmarket safety of all of the Subpart H restricted drugs, FDA has routinely conducted reviews of adverse event reports to monitor for safety concerns. In the case of Mifeprex, FDA investigated the deaths of six U.S. women who developed a fatal infection following treatment with Mifeprex for medical abortion. FDA has determined that in all six of the deaths, the women used a Mifeprex treatment regimen that has not been approved by FDA. Based on its investigations, FDA has concluded that a causal relationship between the use of Mifeprex and the fatal infections has not been established. FDA has also monitored other kinds of adverse events and has concluded that, with the exception of the cases of fatal infection, reported serious adverse events associated with Mifeprex have been within or below the ranges it expected. Additionally, for Mifeprex and the other drugs, FDA has taken similar actions—such as issuing warnings and requesting changes to the product labeling—to communicate safety information to consumers and health care providers.

HHS reviewed a draft of this report and informed us that it did not have general comments. In addition, HHS provided technical comments which we incorporated as appropriate.

Background

The Mifeprex NDA provided for the use of Mifeprex, in combination with another drug, for the medical termination of pregnancy. The treatment regimen described in the NDA involved taking Mifeprex orally, and then taking the drug misoprostol orally 2 days later unless termination of the pregnancy had already occurred.[14] Patients return for a follow-up visit with their prescribing physician 2 weeks later to ensure that the termination of the pregnancy has been completed. The treatment regimen works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.

At the time that the drug sponsor submitted the Mifeprex NDA, in March 1996, mifepristone had already been approved in multiple countries. The drug was first approved for the medical termination of pregnancy in France and China in 1988.[15] It was approved subsequently in the United Kingdom in 1991, in Sweden in 1992, and various other European countries throughout the 1990s. In general, the treatment regimens approved in these countries were similar to those studied in the Mifeprex NDA, though in some cases the specific drug used in combination with mifepristone was different.

FDA Application Review Process

FDA reviews drug applications to determine whether they provide sufficient evidence to demonstrate that a drug is safe and effective for the proposed use, including whether the benefits of the drug outweigh its risks. FDA's formal process for new drug approval begins after a drug sponsor submits an application, typically following a long period of research and development. During a preliminary review, FDA determines whether the application is sufficiently complete to be reviewed and if so, designates it for either standard or priority review, depending on the

[14]Misoprostol is one of several drugs that had been studied in combination with mifepristone for the medical termination of pregnancy because they have been shown to induce uterine contractions. However, it is approved for marketing in the United States for a different indicated use.

[15]The company that discovered mifepristone and manufactured it for marketing in France—Roussel Uclaf—did not want to produce the drug for the U.S. market. Instead, the U.S. sponsor retained a contract manufacturer. For a more detailed discussion of the history of the development of mifepristone for the U.S. market, see: Congressional Research Service, *Abortion: Termination of Early Pregnancy with RU-486 (Mifepristone)*, (Washington, D.C.: 2001).

therapeutic potential of the drug.[16] The agency then assigns a team of reviewers—including medical officers, chemists, statisticians, microbiologists, pharmacologists, and other experts—within the relevant FDA review division. This review team, which is usually led by a medical officer, conducts a comprehensive evaluation of the clinical and non-clinical information in the application including the safety and efficacy data for the drug, the design and quality of the studies used to support the application, and the proposed labeling for the drug and also reviews the results of inspections of the facilities where the drug is manufactured.[17] The review team compiles the results of its analyses and recommends either an approval, approvable, or not approvable action.

FDA managers, usually including the review team's supervisor and senior management within the applicable review division, determine what action to take on an application, based on the recommendations of the review team. These managers examine the review team's analysis and individually decide whether to concur with the recommendation. The final decision on the action the agency should take is usually, but not always, made by the director of the applicable review division. In some cases, actions must be reviewed and agreed to by the relevant FDA office.

This review process may span several cycles. For those applications not approved during the first review cycle—both approvable and not approvable—the second FDA review cycle begins once the sponsor submits an amendment to the application providing responses to the deficiencies FDA identified in its previous review. These amendments often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The responsible review team reviews the information provided by the sponsor, conducts any additional analyses that are required, reviews the results of any additional inspections that have been conducted, and again recommends either an approval, approvable, or not approvable action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the

[16]FDA may grant priority review status when it determines that a drug may provide significant benefits in the treatment, diagnosis, or prevention of a disease as compared to marketed drugs or non-drug therapies, such as surgery, or provide a treatment where no adequate therapy exists.

[17]The non-clinical data in an NDA pertains to, for example a drug's chemistry, manufacturing, and controls as well as its toxicology and pharmacology.

review team and makes its decision on the action to take on the application.

Restricting Drug Distribution and Subpart H Regulations

To address concerns FDA identifies regarding the safe use of a drug, the agency may condition approval by requiring that the sponsor agree to restrict the drug's distribution. FDA has established restricted distribution programs for approved drugs primarily by requiring that a drug's approval be under the restricted distribution provision of Subpart H regulations. According to the scope of the regulations, Subpart H applies to new drugs that "have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments" for the condition.[18] FDA may approve a drug under the restricted distribution provision of these regulations if it meets these criteria and the agency concludes that the drug is effective but can be safely used only if distribution or use is restricted. For example, FDA may require that distribution of a drug be limited to certain facilities or physicians with special training.

As of February 2007, nine drugs—Actiq, Accutane, Lotronex, Mifeprex, Plenaxis, Revlimid, Thalomid, Tracleer, and Xyrem—had either an NDA or supplemental NDA approved under the restricted distribution provision of Subpart H.[19] For each of the drugs, either during the application review process or based on postmarket data, FDA identified concerns about the safe use of the drug that led the agency to apply Subpart H. The drugs were approved to treat a range of conditions, such as breakthrough cancer pain, specific symptoms of narcolepsy, and severe acne.

FDA has also required that drug sponsors agree to restrict the distribution of drugs without imposing Subpart H. Clozaril, Tikosyn, and Trovan are three examples of drugs that have restricted distribution programs that were imposed outside of Subpart H. (See app. I for a table describing drugs FDA has approved with restricted distribution programs and the conditions they are intended to treat). While Clozaril was first approved in

[18]21 C.F.R. § 314.500 (2007).

[19]21 C.F.R. § 314.520 (2007). The sponsor for Plenaxis—approved in 2003 for the palliative care of certain patients with advanced prostate cancer—withdrew the product from the market in 2006. Additionally, three generic versions of Accutane have been approved for marketing under this restricted distribution provision.

1989, FDA imposed distribution restrictions on both Tikosyn and Trovan after Subpart H regulations had been promulgated.

A second approval provision of Subpart H provides FDA with flexibilities that allow the agency to accelerate the approval process for drugs that provide meaningful therapeutic benefits over alternatives for serious or life-threatening illnesses.[20] Specifically, under the provision, FDA may approve a drug on the basis of clinical trials establishing that the drug has an effect on a surrogate endpoint—such as weight gain or reduced occurrence of infections in patients with HIV—that is reasonably likely to predict a clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.[21] This allows FDA to approve a drug before measures of effectiveness that would usually be required for approval are available. However, under this approval provision, drug sponsors are ordinarily required to conduct postmarket studies to confirm and further describe the drug's clinical benefit. As of February 2007, FDA had used this provision to approve 52 drugs, most of which are intended to treat HIV/AIDS or various cancers.

FDA's Role in Postmarket Oversight

Because some risks may not become known until after a drug's approval and use in a wider segment of the population, FDA has a range of postmarket oversight responsibilities once a drug is approved for marketing in the United States. FDA's postmarket oversight responsibilities include assessing sponsors' compliance with requirements for a given drug, such as postmarketing study commitments, adverse event reporting, and restricted distribution requirements. In addition, FDA monitors reported adverse events to assess the postmarket safety of approved drugs and may take action if it develops a concern about a drug's safety.

With regard to postmarketing study commitments, FDA oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report to FDA annually on their progress in meeting the

[20]See 21 C.F.R. § 314.510 (2007).

[21]According to FDA, although some surrogate endpoints are recognized as well-established and have long been a basis for approval (such as change in blood pressure or cholesterol), accelerated approval regulations allow reliance on a "surrogate endpoint that, while 'reasonably likely' to predict clinical benefit, is not so well-established as the surrogates ordinarily used as bases of approval in the past." 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

commitments. FDA requires that sponsors report on the status of these studies in an annual report that also includes updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.[22] FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA also oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with an approved drug.[23] Sponsors must provide in periodic reports (quarterly for the first 3 years after approval and annually thereafter) a narrative summary and analysis of adverse event information. For adverse events that are considered both serious and unexpected,[24] sponsors are required to submit a report—known as a "Postmarketing 15-day Alert Report"—to FDA within 15 calendar days from the time the sponsor was informed of the event. To assess sponsors' compliance with these adverse event reporting requirements, FDA reviews sponsors' reports and conducts inspections of the sponsors' reporting policies and procedures.

For drugs approved under the restricted distribution provision of Subpart H, FDA oversees sponsors' compliance with the restrictions placed on the drugs' distribution or use. To assess compliance with restrictions, FDA reviews information such as summaries of sponsors' distribution programs in annual reports and in some cases separate reports required by the agency to provide details and updates on distribution programs. In addition, FDA may conduct inspections of a sponsor's corporate headquarters, manufacturing sites, or contractors, such as specialty distributors, to evaluate whether distribution policies and procedures comply with the approved restrictions for a given drug. If FDA identifies deficiencies during an inspection, it may issue a formal citation—known as a Form FDA 483. In addition, FDA may communicate less serious findings as written or oral "observations" or "recommendations."[25]

[22]See 21 C.F.R. § 314.81 (2007).

[23]See 21 C.F.R. § 314.80 (2007).

[24]Unexpected events are those that are not included in the current labeling for a drug.

[25]FDA uses the same reporting scheme—noting citations, observations, or recommendations— for its inspections to assess sponsor compliance with adverse event reporting.

To monitor postmarket safety of approved drugs, FDA reviews clinical literature, routinely evaluates the available data on reported adverse events, and conducts investigations of the nature and patterns of these events. FDA compiles data from sponsor's reports on adverse events, along with data from voluntary reports submitted to the MedWatch program, in its Adverse Event Reporting System (AERS) database.[26] FDA safety evaluators analyze data from AERS and in the clinical literature to detect signs of potential safety concerns. These evaluations may reveal the need for further studies of a drug or may result in FDA action to ensure the safety of the drug.[27]

If FDA identifies problems with a sponsor's compliance with agency requirements or identifies postmarket safety concerns, the agency can take a range of actions to address the concern and communicate safety information to healthcare providers and the public. For example, FDA may revise the restrictions on a drug's distribution, request changes to a drug's labeling, issue patient advisories or public health alerts, or request that a sponsor issue letters to health care providers or pharmacists to alert them to safety concerns. FDA may also issue a regulatory letter citing violations of laws or regulations. Typically, FDA issues a Warning letter for violations that may lead FDA to pursue further enforcement action if not corrected or issues an untitled letter for violations that do not meet this threshold. FDA also has the authority to withdraw a drug's marketing approval for safety-related and other reasons,[28] although it rarely does so. Additionally,

[26]MedWatch is a voluntary reporting program through which health professionals and consumers can report adverse reactions, product problems, and use errors related to drugs and other products approved by FDA.

[27]GAO has previously reported on and made recommendations regarding FDA's postmarket oversight of approved drugs. See GAO, *Drug Safety: Improvements Needed in FDA's Postmarket Decision-making and Oversight Process*. GAO-06-402. (Washington, D.C.: Mar. 31, 2006).

[28]21 U.S.C. § 355(e).

Subpart H regulations establish an expedited process for withdrawing a drug's marketing approval, in certain circumstances.[29]

FDA Approved Mifeprex under the Subpart H Restricted Distribution Provision After Concluding That Clinical Evidence Supported Its Safety and Efficacy

FDA approved Mifeprex after three review cycles. In its initial review, FDA concluded that reliance on historical controls in three key clinical trials was appropriate and consistent with FDA regulations and that the available data supported the safety and efficacy of the drug. In an approvable letter, FDA notified the sponsor that it needed to provide additional data and more detail on its proposal to restrict the drug's distribution before an approval decision could be made. A second review cycle began when the sponsor submitted data responding to this letter. The agency issued a second approvable letter after finding that new data confirmed Mifeprex's safety and efficacy but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. FDA further concluded that the drug was a candidate for approval under Subpart H. In the final review cycle, FDA concluded that the sponsor's revised distribution plan and other revisions were sufficient to address FDA's comments. FDA also concluded that Mifeprex met the scope of Subpart H and that approval under the restricted distribution provision of Subpart H was necessary to ensure that only qualified physicians prescribed the drug. On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H with several restrictions and two postmarketing study commitments. (See table 1 for a timeline of key events in the Mifeprex approval process.)

[29]Under Subpart H regulations, FDA may withdraw a drug's marketing approval after providing for a hearing, in the following circumstances; (1) a postmarketing clinical study fails to verify clinical benefit; (2) the sponsor fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) the sponsor fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use. 21 C.F.R. § 314.530 (2007).

Table 1: Timeline of Key Events in FDA's Approval of Mifeprex

Date	Event
First review cycle	
March 1996	The sponsor submitted a new drug application (NDA) for the use of Mifeprex in combination with the drug misoprostol for the medical termination of intrauterine pregnancy.
July 1996	FDA Reproductive Health Drugs Advisory Committee meeting.
September 1996	FDA issued an approvable letter listing issues that the sponsor needed to address before the application could be approved.
Second review cycle	
August 1999	After delays securing a manufacturer, the sponsor completed its responses to FDA's 1996 approvable letter.
February 2000	FDA issued a second approvable letter, listing issues that the sponsor needed to address prior to approval.
Third review cycle	
March 2000	The sponsor completes its responses to FDA's second approvable letter.
September 2000	FDA approved Mifeprex under the restricted distribution provision of Subpart H.
November 2000	Distribution of Mifeprex began in the United States.

Source: GAO analysis of FDA and drug sponsor data.

FDA's Initial Review Cycle and Approvable Action (March to September 1996)

FDA's initial review began when the drug sponsor submitted the Mifeprex NDA in March 1996. After conducting a preliminary review of the NDA, FDA designated the application for priority review, establishing a goal that the agency would issue an action letter within 6 months. FDA's rationale for the designation was that as the first drug that would be approved for its particular indication, Mifeprex was a therapeutic advance because women using the drug could potentially avoid the risks of surgery and anesthesia involved in a surgical termination of a pregnancy.

FDA assigned a team of reviewers within the Division of Reproductive and Urologic Drug Products to review the evidence in the Mifeprex NDA. The key safety and efficacy data in the NDA consisted of three historically controlled clinical trials, two conducted in France and one conducted in the United States. These trials studied the Mifeprex treatment regimen—mifepristone in combination with misoprostol—in a total of more than 4,000 women. At the time the NDA was submitted, the French trials were complete and the U.S. trial was ongoing. As a result, during the first review cycle, the review team analyzed the complete safety and efficacy data from the French clinical trials, but only summary data on serious adverse events

from the U.S. clinical trial. FDA reviewers also considered results from other trials conducted in Europe from 1983 through 1996 in which mifepristone was studied either alone or in combination with misoprostol or similar drugs. In addition, the review team considered safety information from extensive postmarketing experience in Europe, including a postmarket safety database containing information on women who had used mifepristone. Lastly, the review team considered the non-clinical data in the application, including data on the drug's chemistry and manufacturing.

In its review of the Mifeprex data, FDA reviewers determined that the reliance on historical controls in the key clinical trials was appropriate and consistent with FDA regulation. According to FDA, historical control designs can make it more difficult to evaluate which effects can be attributed to the drug being studied.[30] However, FDA regulations list historical controls as an acceptable type of control when the natural history of the condition being treated is well-documented and when the effects of the drug are self-evident.[31] In the case of the Mifeprex NDA, FDA determined that the historically controlled trials provided substantial evidence of safety and efficacy because the outcomes of women taking the Mifeprex regimen were compared with the well-documented data on the natural course of pregnancy, including rates of miscarriage, and the effect of the drug—termination of a pregnancy—was obvious.[32]

To assist the review team in its assessment of Mifeprex, FDA convened the Reproductive Health Drugs Advisory Committee in July 1996 and asked the members to examine the data and vote on their conclusions regarding the drug's safety and efficacy. Six of the eight voting members voted, with

[30]See FDA, *Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Tials* (Rockville, Md.: May 2001).

[31]21 C.F.R. § 314.126(b)(2)(v) (2007). The regulation also states that studies that are "adequate and well-controlled" provide the primary basis for determining whether there is "substantial evidence" in support of the claims of effectiveness for new drugs. Among other things, an adequate and well-controlled study provides sufficient details of study design, conduct, and analysis to allow critical evaluation, and the design must permit a valid comparison with a control to provide a quantitative assessment of the drug's effect.

[32]FDA has cited examples of other drugs that have relied upon historical controls. According to FDA, for contraceptives the effect of the drug can be compared to the well-documented rate of pregnancy in sexually active women between the ages of 15 and 35 in the absence of contraception. For example, FDA approved the contraceptive drug products Lybrel, Implanon, Yaz, and NuvaRing on the basis of historically controlled clinical trials.

two abstentions, that the available evidence demonstrated that the benefits of the regimen outweighed its risks for the proposed indication in the United States. However, the members agreed unanimously that FDA should provide the final safety and efficacy data from the U.S. clinical trial for their review. The advisory committee also discussed the basic elements of a voluntary restricted distribution system proposed by the drug's sponsor, which would require that Mifeprex be distributed directly to physicians, that prescribing physicians meet certain training requirements, and that patients meet certain conditions before receiving the drug. The advisory committee voted unanimously that they agreed with the concept of restricting distribution of the drug but had reservations about how the proposed system would assure that physicians had adequate credentials. The members recommended that the sponsor conduct postmarket studies to address six unanswered questions about the treatment regimen and the distribution system. The members also provided extensive comments on the draft labeling proposed by the sponsor.

The FDA review team concluded that the NDA was approvable, based on its assessment of the clinical and non-clinical data and the input from the advisory committee. The medical officer leading the review team concluded that the available clinical data indicated "that medical abortion can be safely delivered in a wide variety of United States settings." The data from the French trials showed the treatment to be roughly 95 percent effective at terminating pregnancy through 49 days gestation. The data from the French clinical trials also showed that almost all patients experienced some side effects—such as uterine cramping and bleeding—most of which were expected based on the way the drug works. Though serious adverse events were considered rare, some women experienced bleeding that required medical intervention, and approximately 0.2 percent of patients required transfusion. The medical officer concluded that the preliminary U.S. data on adverse events did not appear to differ significantly from the French trials.[33]

[33]The medical officer noted that it was only possible to make general comparisons across these events because definitions and reporting requirements were different in the two countries. Additionally, while the sponsor had not yet completed its analysis of the safety and efficacy data from the U.S. clinical trial, information from the studies was forwarded to the sponsor weekly. The medical officer concluded, based on preliminary examination of this information, that the final results of the U.S. trials were likely to be similar to the results of the French trials.

In September 1996, FDA issued an approvable letter for the use of Mifeprex in combination with the drug misoprostol for the termination of intrauterine pregnancy up to 49 days gestation. In memos documenting concurrence with the review team, and in the approvable letter itself, FDA management outlined the clinical and non-clinical issues the sponsor needed to address prior to approval. First, the full data from the U.S. clinical trial were needed to establish safety and efficacy of the Mifeprex regimen in the U.S. health care setting. Second, FDA agreed with the sponsor's proposal to limit the drug's distribution, but the sponsor had not yet submitted sufficient detail on how it would be implemented to allow for the plan to be fully evaluated.[34] Third, the drug labeling proposed by the sponsor needed to be revised to provide more information on the treatment and to address comments from the advisory committee. Fourth, the sponsor would need to commit to pursue the postmarket studies suggested by the advisory committee. Finally, the sponsor would need to address certain deficiencies in chemistry and manufacturing data identified in FDA's review.

FDA's Second Review Cycle and Approvable Action (August 1999 to February 2000)

FDA's second review cycle for the Mifeprex NDA officially began once the sponsor had completed its responses to the first approvable letter. However, these responses were delayed because of difficulties the sponsor encountered in securing a manufacturer for the drug product. In the interim, the sponsor submitted a range of data to FDA, including the final safety and efficacy results from the U.S. clinical trial, updated safety data from other trials of mifepristone and international postmarketing experience with the drug, formal revisions of the product labeling, and outstanding chemistry and manufacturing data. In August 1999, the sponsor completed its responses to the approvable letter by submitting an overview of the key principles of the restricted distribution system as well as responses to the postmarketing study commitments. At the time of this submission, the sponsor was still working with its planned distributor on the details of the restricted distribution system.

Based on the updated data, the review team recommended approval for the Mifeprex NDA once the sponsor had clarified the details of the drug's distribution, revised the drug labeling, and addressed deficiencies in the

[34]FDA management's concurrence memos noted that because the sponsor had voluntarily proposed a restricted distribution system, imposing restrictions through Subpart H regulations did not appear warranted.

chemistry and manufacturing data. The medical officer concluded that the final results from the U.S. clinical trial were acceptable and confirmed the results of the French trials that the regimen was safe and effective.[35] The medical officer concluded that the comments from the July 1996 advisory committee meeting were fully considered and, to the extent possible, implemented.[36] The medical officer also concluded that additional detail was needed to determine whether the sponsor's proposed distribution plan was sufficient. The non-clinical reviews during this review cycle—which included inspections of manufacturing facilities[37]—identified deficiencies in the drug's chemistry data and manufacturing processes that needed to be addressed, as well as sections of the drug's labeling that needed to be revised.

In January 2000, the sponsor submitted a more detailed plan describing how the proposed distribution restrictions would be implemented. The plan had three key elements. First, the Mifeprex regimen would only be administered under the supervision of qualified physicians who had agreed to provide the treatment according to several guidelines. Specifically, prescribing physicians would be required to attest to being able to accurately assess the duration of a pregnancy, diagnose an ectopic pregnancy,[38] and assure that patients have access to appropriate follow up care if needed to manage complications. The physicians would also need to agree to fully explain the procedure to each patient and obtain her

[35]The U.S. clinical trial data showed the treatment to be 92 percent effective for terminating pregnancy through 49 days gestation, which was slightly lower than the 95 percent from the French trials. Adverse event rates were also slightly higher in the U.S. trials. The medical officer attributed these differences to the relative inexperience of U.S. clinicians with the treatment. In addition, the medical officer concluded that the updated information from international studies, postmarket experience, and the published literature was consistent with the results from the U.S. and French trials.

[36]In November 1999, FDA provided advisory committee members the final results from the U.S. clinical trial for their review and comment. FDA did not receive any comments from the members on these results.

[37]The drug substance (mifepristone) in the Mifeprex product was manufactured by the Shanghai Haulian Pharmaceutical Co., Ltd., with the manufacturing facilities located in China. Initial FDA inspections found the manufacturer not in compliance with FDA's good manufacturing practice standards.

[38]Ectopic pregnancy—which occurs when a fertilized egg improperly implants outside of the uterus—is a contraindication for receiving the Mifeprex regimen. Accurate screening to ensure that patients with an ectopic pregnancy do not receive the treatment was a concern because a ruptured ectopic pregnancy is a life-threatening condition and its symptoms are similar to the side effects of the Mifeprex regimen.

signed consent, record the unique product serial number for tracking purposes, and report any serious adverse event or on-going pregnancy to the sponsor. Second, the drug would only be distributed directly to physicians after an authorized distributor had verified that the physician had registered with it and had a signed attestation on file. Third, patients would be required to meet certain conditions before receiving the drug, such as signing a patient agreement attesting to her understanding of the potential complications of the treatment.

FDA management concluded that the proposed distribution plan did not provide for adequate training and certification of prescribing physicians and needed to be revised before the NDA could be approved. In February 2000, FDA issued a second approvable letter for Mifeprex, notifying the sponsor that it needed to revise its proposed distribution plan, address deficiencies in the drug's chemistry data and manufacturing, and revise the drug's labeling. The letter also stated that FDA had considered the application under the restricted distribution provision of Subpart H and that distribution restrictions would be necessary in order to assure the safe use of the drug. The approvable letter further reminded the sponsor of its commitment to pursue postmarketing study commitments to address questions that were raised at the time of the advisory committee meeting.

FDA's Final Review Cycle and Marketing Approval for Mifeprex (March to September 2000)

In March 2000, the sponsor submitted its complete response to FDA's February 2000 approvable letter. This submission included updated safety data from ongoing trials and international postmarket experience, international product labeling, and revisions to the distribution plan. The sponsor also provided additional data and revisions—including updated chemistry and manufacturing data, a revision to the distribution plan, and revised labeling—to address comments from FDA that arose during the review cycle. The agency's review of these submissions included multiple meetings and teleconferences with the sponsor and input from a consultant who was a special government employee (SGE) and a member of the Reproductive Health Drugs Advisory Committee.[39]

[39]According to FDA, it is not uncommon for the agency to consult with members of its advisory committees who have special expertise in a particular drug under review. Generally, an SGE is defined as an officer or employee who is retained, designated, appointed, or employed by the government to perform temporary duties, with or without compensation, for not more than 130 days during any period of 365 consecutive days. 18 U.S.C. § 202(a).

During the final review cycle, FDA's deliberations—which involved a wide range of agency staff and management, including at times the Commissioner—focused on four key issues: whether prescribing physicians should be required to participate in a formal training and certification program, whether to require that approval be under Subpart H, what conditions of use should be specified, and what postmarketing study commitments would be needed to assure the safe use of the drug.

- Physician Training: In its deliberations, FDA considered requiring that physicians participate in specific training and have their qualifications certified before being allowed to prescribe Mifeprex, as opposed to relying on the sponsor's proposed system of self-attestation. However, FDA concluded that such a requirement was not necessary. FDA officials told us that the agency determined that its concern about ensuring that prescribers were adequately qualified could be addressed by requiring that the sponsor make educational materials and training programs readily available and requiring that prescribing physicians sign an agreement attesting to their qualifications. The SGE consultant agreed with this conclusion. FDA officials also told us that the agency wanted to minimize the burden that the restricted distribution program would place on providers and patients by requiring only what was necessary to address safety concerns.[40]

  In July 2000, the sponsor submitted its revised distribution plan. This plan addressed FDA's comments by providing increased emphasis in the product labeling on the educational materials and trainings available to physicians and the importance of participating in the training. The other key elements of the plan—including the specific qualifications that physicians were required to meet and agreements regarding discussing the treatment and adverse event reporting—were essentially unchanged from those the sponsor proposed in its January 2000 plan.

- Approval under Subpart H Regulations: FDA had maintained through the first two review cycles that distribution restrictions would be required for Mifeprex. However, minutes from meetings between FDA and the sponsor indicate that the agency was still considering whether it was necessary to impose those restrictions under Subpart H during the final review cycle. During the second review cycle, FDA had concluded that the restricted

[40]Subpart H regulations state that any restrictions imposed will be commensurate with the specific safety concerns presented by the drug product. 21 C.F.R. § 314.520(b) (2007).

distribution provision could be applied to Mifeprex.[41] FDA eventually concluded that it would be necessary to do so. In its documented rationale for this conclusion, FDA stated that the drug met the scope of the regulations because the termination of an unwanted pregnancy is a serious condition, and that the drug provided a meaningful therapeutic benefit over existing therapies by allowing patients to avoid the procedure required with surgical termination of pregnancy. FDA officials told us that the agency has broad discretion to determine which conditions or illnesses may be considered serious or life threatening, and that in the case of Mifeprex it considered the potential in any pregnancy for serious or life-threatening complications—such as hemorrhage—in its determination.[42] Additionally, FDA concluded that Mifeprex could only be used safely if distribution was limited to physicians who could assess the duration of a pregnancy, diagnose an ectopic pregnancy, and provide patients with access to surgical intervention if necessary.

Throughout the approval process, the sponsor was opposed to approval under Subpart H. Specifically, the sponsor argued that the drug did not fit within the scope of Subpart H because pregnancy itself is not a serious or life threatening illness. The sponsor also argued that the intent of the restricted distribution provision was to allow for restricted distribution of highly toxic or risky drugs, and that Mifeprex did not fit this description.[43] The sponsor also expressed concern that approving the drug under Subpart H could unfairly mark Mifeprex as risky and deter women from using the drug. Lastly, the sponsor held that imposing Subpart H was unnecessary because it had voluntarily committed to the distribution

[41]FDA had also noted that approving the drug under Subpart H would allow the agency to impose similar restrictions on any future generic mifepristone products approved for the same indication. The patent for Mifeprex expired in October 2004, but as of May 2008, no generic versions of mifepristone have been approved for marketing.

[42]The terms "serious" and "life-threatening" are not defined in Subpart H regulations, but were discussed in the preambles to the proposed and final rules. In its proposed rule, FDA stated that the seriousness of a disease is a matter of judgment, but generally is based on its impact on survival, day-to-day functioning, or other factors, and provided examples of conditions that could be within the scope of the regulation. FDA noted that many diseases or conditions can be serious for some populations in some or all of their phases and explicitly reserved the discretion to determine whether the regulations were applicable to a given product. See 57 Fed. Reg. 13234-5 (Apr. 15, 1992), 57 Fed. Reg. 58942, 58946 (Dec. 11, 1992); See also 21 C.F.R. §§ 312.34, 312.81 (2007), and FDA, *Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review* (Rockville, Md.: Jan. 2006).

[43]In support of its arguments about the intent of the regulations, the sponsor cited the pertinent language from preambles to the proposed and final rules. See footnote 42.

restrictions requested by FDA. However, in a September 2000 letter to FDA, the sponsor agreed to FDA's requirement that approval be under Subpart H, while noting that it still believed that applying these regulations to Mifeprex was not appropriate.

- Conditions of Use: FDA reviewed data and held multiple meetings with the sponsor regarding the specific conditions of use that should be required for Mifeprex. For example, FDA deliberated about whether it was necessary to require that prescribing physicians possess the ability to perform follow-up surgical interventions in the event that it was necessary to manage complications. The sponsor maintained that such a requirement was inconsistent with the practice of medicine, because management of incomplete miscarriages was routinely handled by referring patients to outside providers with specialized surgical or emergency care training. On this issue, FDA concluded that access to follow-up care could be ensured by requiring adequate information in the labeling and requiring that physicians attest to having made arrangements for their patients to have access to any needed surgical or emergency care. The SGE consultant agreed with FDA's conclusion. FDA disagreed with the sponsor on other suggested conditions of use. For example, the sponsor provided data to support allowing patients to self-administer the misoprostol dose at home, instead of requiring them to return to their prescribing physicians. FDA concluded that the available data did not support the safety of home use of misoprostol and that such use should not be included in the final product label. As a part of its deliberations about the conditions of use, FDA also concluded that approved labeling should include a medication guide to provide patients with information about the risks and benefits of the drug and the approved conditions of use and treatment regimen.[44]

- Postmarketing Study Commitments: In both the September 1996 and February 2000 approvable letters, FDA had reminded the sponsor of its commitment to conduct a series of six postmarket studies to address comments raised in the 1996 advisory committee meeting. FDA reviewed data and met with the sponsor during the final stages of its review to revisit these commitments in light of experience gained with the treatment regimen since the advisory committee meeting, concerns about potential infringement on the privacy of patients, and the potential resources needed to fulfill all six commitments. FDA concluded that the originally proposed commitments could be sufficiently addressed in two redesigned

[44]FDA may require that a drug be distributed with a medication guide that provides patients with information about the safe and effective use of the drug. See 21 C.F.R. pt. 208 (2007).

studies. The first was a study on the safety outcomes of a group of patients receiving the treatment under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention when necessary. The second was a surveillance study to determine the outcomes of ongoing pregnancies that were not surgically terminated after a failure of the Mifeprex regimen, including the health of any children born. FDA also concluded that the outstanding questions could be incorporated into the two postmarket studies and an audit of signed patient agreement forms.

Once the sponsor had addressed the issues that FDA raised during the third review cycle, both the review team responsible for the Mifeprex NDA and FDA management concluded that the drug should be approved. The medical officer concluded that the updated safety data did not reveal any new issues that would change the ratio of benefit-to-risk for the drug. The medical officer also reviewed revised product labeling related to the distribution of the drug. Based on these reviews, the medical officer recommended approval of the application. The non-clinical reviews during this review cycle included additional inspections of manufacturing facilities. After the sponsor had addressed several issues, including deficiencies identified in a second inspection of the drug manufacturing facilities, the non-clinical reviewers also recommended approval of the application. FDA management concurred with the recommendations of the review team that the Mifeprex NDA should be approved.

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H. The sponsor began distribution of Mifeprex in November 2000. FDA approved the drug with the two postmarketing study commitments discussed above and with several key restrictions on distribution. First, prescribing physicians must sign a prescriber's agreement attesting to possessing the training and skills needed to administer the treatment regimen, and also agreeing to provide patients with the approved medication guide. They must also attest that they will fully discuss the treatment with patients and report to the sponsor any serious adverse events or ongoing pregnancies that are not terminated after a failure of the Mifeprex regimen. Second, the drug must be distributed directly to prescribing physicians by an authorized distributor only after the distributor has verified that the physician has a signed agreement on file. Third, patients must sign a patient agreement attesting to having read, discussed, and understood the risks and potential complications of the treatment. For a more detailed list of the individual components of the restricted distribution program for Mifeprex, see

appendix II. For a copy of the approved prescriber's agreement, see appendix III.

Approval Process for Mifeprex Was Generally Consistent with That of the Other Eight Subpart H Restricted Drugs

Although each drug had unique risks and benefits, the approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs. Each of the drugs had unique risks and benefits that were specific to their indication and target populations. For some of the drugs, the safety issues that prompted FDA to apply Subpart H were similar, with the potential for causing birth defects, the potential for liver or other serious toxicities, and appropriate patient selection being the most common issues. However, there were also safe use concerns that were unique to particular drugs. For example, for Mifeprex, ensuring patient access to follow-up care was a key safety concern, while for Actiq a key concern was ensuring that children did not accidentally ingest the drug.[45] Each of the drugs represented potential advances in the treatment of their targeted condition and in two cases—Mifeprex and Xyrem—the drug was the first approved to treat that condition. (See app. I for a table including each of the Subpart H restricted drugs and their approved indications.)

One common element across the approval processes for the Subpart H restricted drugs was that for seven of the drugs, including Mifeprex, FDA needed to evaluate potential limitations in key clinical data supporting the NDA. Specifically, with the exception of Accutane and Lotronex, the drugs were approved on the basis of studies without concurrent controls or data that were limited by relatively small sample sizes or data collection issues.[46] FDA approved the Mifeprex NDA on the basis of historically controlled clinical trials that studied the drug in several thousand patients. FDA concluded that the use of historical controls was not a limitation

[45]Actiq contains the controlled substance fentanyl in a lozenge formulation intended to allow for more rapid delivery of the medication for pain management in patients who have developed a tolerance. Because of the formulation there are concerns that Actiq may be perceived by children as a lollipop.

[46]Both Accutane and Lotronex were approved under Subpart H after they had first been marketed in the United States. In the case of Lotronex, the sponsor withdrew the drug from the market in 2000 because of safety concerns. In 2002, FDA approved a supplemental NDA under Subpart H, allowing the drug to be marketed with a restricted distribution program and substantially more limited indication. For Accutane, which was originally approved for marketing in 1982, FDA approved a supplemental NDA under the restricted distribution provision of Subpart H in 2005 in order to require a more formal restricted distribution program that linked Accutane prescribing and dispensing to pregnancy testing results.

because the course of pregnancy was well-documented and the effect of the treatment was self-evident. Revlimid, Thalomid, Plenaxis, and Xyrem were also each approved on the basis of data that included at least one key clinical study that lacked a concurrent control.[47] In contrast to the Mifeprex data, FDA concluded that the lack of concurrent controls in these studies was a weakness because data on the course of the disease in a comparable population was not available to be used as a reliable historical control. For example, Thalomid was approved on the basis of clinical trial data from the published literature as well as a series of retrospective case studies for several dozen patients.[48] Additionally, five of the drugs—Actiq, Revlimid, Thalomid, Tracleer, and Xyrem—were approved on the basis of key clinical studies with relatively small sample sizes of several hundred patients or less. Finally, for Actiq, Plenaxis, Thalomid, and Xyrem, FDA identified data collection issues, such as incomplete documentation, in some of the key data sources.

Another common element was that for six of the drugs, including Mifeprex, FDA issued at least one prior action letter before ultimately approving the drug for marketing. FDA issued one approvable letter before ultimately approving Thalomid and Tracleer. Both Mifeprex and Xyrem received two approvable letters. In some cases the types of issues FDA cited—such as insufficient safety or efficacy data, the need for additional information on the restricted distribution system, or chemistry and manufacturing issues—were similar. For all four of these drugs, the adequacy of proposed distribution restrictions was a significant issue. For Xyrem, FDA's initial approvable action was also linked to the sufficiency of the data provided in the application. FDA issued not approvable letters for both Actiq and Plenaxis prior to their eventual approval. In the case of Actiq, FDA cited multiple deficiencies, such as reliance on a key clinical study with flaws and an inadequate plan for risk management. For Plenaxis, FDA initially concluded that the risks of the drug exceeded its

[47]FDA approved Plenaxis on the basis of one uncontrolled clinical trial in the indicated population—men with advanced symptomatic prostate cancer—and three concurrently-controlled clinical trials in men with less advanced prostate cancer. FDA approved Xyrem on the basis of one uncontrolled key safety trial, and two concurrently-controlled clinical trials.

[48]FDA considers such case studies to be historically controlled. In this case, the reviewing division concluded that the data were not sufficient to demonstrate the safety and efficacy of Thalomid. However, that decision was overridden by both the Director of the relevant FDA office and the Director of FDA's Center for Drug Evaluation and Research, based on their individual analyses of the available data.

benefits because of the potential for severe, systemic allergic reactions in patients.

As a result of these complexities, the approval process for the Subpart H restricted drugs was typically longer than the process for other drugs. Across the seven drugs with NDAs approved under Subpart H, an average of almost 25 months elapsed from the time that the sponsor submitted its NDA to the time FDA approved the NDA. The length of time to approval ranged from almost 9 months for Revlimid to more than 54 months for Mifeprex. In comparison, in analyses conducted for our 2006 report on new drug development, we found that it took FDA on average almost 18 months to approve NDAs submitted from 1996 through 2002.[49]

We also found that the types of distribution restrictions FDA imposed on Mifeprex were similar to those imposed on the other Subpart H restricted drugs, though the specifics of the restrictions depended on FDA's safe use concern for the drug.[50] (See table 2.) For all of the drugs except Actiq, FDA required some form of program enrollment or registration process. For example, for Mifeprex and three other drugs, FDA required that patients sign written agreements and that physicians enroll in a prescribing program and attest to their qualifications. For five of the drugs, FDA required formal registries of all prescribing physicians and patients.[51] Additionally, for seven of the drugs, FDA required that distribution be limited to authorized distributors or pharmacies.[52] And for eight of the

[49]See, GAO, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49. (Washington, D.C.: Nov. 17, 2006). In contrast, the drugs approved under the surrogate endpoint provision of Subpart H have generally been approved more rapidly than drugs approved under the restricted distribution provision of Subpart H and than drugs approved outside of Subpart H.

[50]Additionally, except for Plenaxis, FDA convened a meeting of the relevant advisory committee prior to each drug's approval under Subpart H to obtain expert input regarding the appropriate actions to address the agency's safe use concerns, including the distribution restrictions that should be required. The advisory committee meetings that FDA has held for the drugs Accutane and Lotronex occurred after each drug was first marketed in the United States, but prior to their approvals under Subpart H.

[51]FDA has used various types of registries as a mechanism to collect data on patients, providers, and others as a tool for monitoring outcomes of interest.

[52]Two of the drugs—Actiq and Xyrem—were approved as controlled substances and therefore subject to the restrictions imposed by the Controlled Substances Act. Requirements imposed under this act are enforced by the Drug Enforcement Administration and are distinct from the distribution restrictions imposed on these drugs by FDA under Subpart H. See, e.g., 21 U.S.C. § 822; 21 C.F.R. § 1301.11 (2007).

drugs, FDA required that the sponsor establish a process to ensure that dispensing or distribution of the drug was contingent on verification that physicians and others had enrolled or registered in the distribution program, or that patients had complied with certain safety measures. FDA also required that all of the sponsors implement some form of educational program for patients, prescribers, or pharmacists, though FDA did not require that prescribing physicians participate in formal training for any of the drugs. For six of the nine drugs, FDA required that the sponsor report periodically to the agency specifically on implementation of their restricted distribution programs. For seven of the drugs, FDA required that sponsors report to the agency on specific adverse events—such as fetal exposures or liver toxicity—more frequently than is required for other drugs. In the case of Mifeprex and Xyrem, at the time the drugs were approved, FDA did not require that the sponsors submit additional adverse event reports beyond those required for all approved drugs, but did require that physicians agree to report specific types of adverse events to the sponsor.

Table 2: Selected Features of Restricted Distribution Programs Imposed by FDA at Time of Approval under Subpart H

Features Required at Approval	Mifeprex (mifepristone)	Lotronex (alosetron hydrochloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenalidomide)	Accutane (isotretinoin)
Program enrollment or registration[a]	✓	✓		✓	✓	✓	✓	✓	✓
Limited distribution channels[b]	✓			✓	✓	✓	✓	✓	✓
Dispensing or distribution contingent on verification[c]	✓	✓		✓	✓	✓	✓	✓	✓
Sponsor developed educational programs[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reporting specific to implementation of restricted distribution program		✓	✓	✓	✓		✓		✓
Additional adverse event reporting by the sponsor[e]		✓	✓	✓	✓		✓	✓	✓

Source: GAO analysis of FDA data.

[a]Program enrollment or registration requirements varied across the drugs. For Accutane, Lotronex, Mifeprex, and Plenaxis, FDA required that physicians enroll in a prescribing program and attest to their qualifications. For Accutane, Revlimid, Thalomid, Tracleer, and Xyrem, FDA required formal registries of all prescribing physicians and patients. FDA also required registration of pharmacies, wholesalers, or distributors for Thalomid, Revlimid, and Accutane.

[b]The specific limitations imposed on distribution channels varied across the drugs, and in some cases more than one limitation was required. These limitations included, for example, requiring that a drug only be distributed directly to prescribing physicians, allowing only authorized distributors or wholesalers to ship a drug, and allowing only registered or centralized pharmacies to dispense a drug.

[c]The verification mechanisms varied across the drugs. For example, for Mifeprex, an authorized distributor must verify that a physician has a signed prescriber agreement on file before distributing the drug. For Lotronex, before dispensing and drug, pharmacists must verify that prescriptions include a sticker that is only available to physicians enrolled in the prescribing program. For Accutane, Revlimid, and Thalomid, a registered pharmacy is required to confirm prescription authorizations and that patients have complied with requirements to use one or more methods of contraception before dispensing the drug.

[d]In general, sponsors were required to develop educational materials (such as patient information videos) for patients, and make educational materials and training programs readily available to prescribing physicians, pharmacists, and other groups involved in the restricted distribution program. For some of the drugs, dispensing pharmacists were required to participate in formal training. At the time of Subpart H approval, FDA required medication guides for all of the drugs except Actiq, Plenaxis, and Thalomid.

[e]Sponsors for seven of the drugs were required to submit 15-day alert reports on specific adverse events. Sponsors of four of the drugs were required to provide updates more frequently than typically required for events related to FDA's safe use concern for the drug. For Mifeprex, as part of their prescriber agreement, physicians agreed to report ongoing pregnancies, hospitalizations, transfusions, and other serious events to the sponsor. For Xyrem, FDA required that physicians agree to collect and report to the sponsor information on specific adverse events and inappropriate use of the drug.

Finally, eight of the nine Subpart H restricted drugs were approved with two or more postmarketing study commitments.[53] Each of these had at least one commitment that involved developing a postmarket study to monitor adverse events or patient outcomes of interest for that drug. The number of study commitments FDA required ranged from 2 to 10, depending on the drug. Additionally, for most of the drugs, including Mifeprex, the study protocols for the various commitments had not been finalized at the time of approval.

[53]FDA's approval of Accutane under Subpart H through a supplemental NDA did not include any postmarket study commitments.

FDA's Postmarket Oversight of Mifeprex Has Been Consistent with the Agency's Oversight of the Other Subpart H Restricted Drugs

The actions FDA has taken to oversee Mifeprex have been consistent with the actions it has taken to oversee the other Subpart H restricted drugs. FDA has relied primarily on information submitted by the sponsors of all the Subpart H restricted drugs and inspections for three of the drugs to oversee compliance with restricted distribution requirements. FDA has also relied on updates submitted by these sponsors to oversee compliance with postmarketing study commitments and has found that most have unfulfilled commitments. To oversee compliance with adverse event reporting requirements, FDA has reviewed a variety of safety information including reports submitted by the sponsors of all nine of the drugs restricted under Subpart H and has conducted inspections to evaluate compliance with reporting of adverse events for eight of the drugs. As a result, for most of the drugs, FDA has identified deficiencies in compliance with adverse event reporting requirements. To oversee reported adverse events FDA has used similar methods—such as monitoring, investigating, and addressing safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. As a result of its oversight of safety data, FDA has identified postmarket safety concerns for most of the drugs and has used a variety of methods to communicate safety information to health care providers and the public. (See table 3 for an overview of FDA's postmarket oversight of these drugs.)

Table 3: Selected Features of FDA's Oversight of Postmarket Safety for Drugs Approved under Subpart H, as of May 2008

Oversight Activities and Findings	Mifeprex (mifepristone)	Lotronex (alosetron hydrochloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenalidomide)	Accutane (isotretinoin)
FDA has completed inspection(s) to oversee compliance with distribution restriction requirements[a]	✓				✓	✓			
FDA has classified at least one postmarketing study commitment as unfulfilled[b]	✓	✓	✓	✓	✓		✓	✓	n/a
FDA has conducted inspection(s) to oversee compliance with adverse event reporting requirements[c]	✓	✓	✓	✓	✓	✓	✓		✓
FDA has identified a postmarket safety concern leading to communication of new safety information to public or health care providers[d]	✓	✓	✓	✓	✓	✓		✓	✓

Source: GAO analysis of FDA data.

Note: FDA provided or confirmed data on these selected features of oversight through May 2008.

[a]In May 2008, FDA officials told us that they had conducted such inspections for three additional drugs. However, the reports from those inspections were not yet available. Inspections were in addition to report review.

[b]FDA classifies unfulfilled postmarketing study commitments as ongoing, pending, delayed, released, or terminated; FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarketing study commitments and has submitted the final report for the third and final commitment.

[c]Inspections were in addition to report review conducted for all of the drugs. In the case of Revlimid, FDA inspected Celgene—the sponsor of both Revlimid and Thalomid—before Revlimid was approved in December 2005.

[d]Communication of new safety information includes activities such as changing product labeling, issuing Public Health Advisories and Safety Alerts, and distributing letters to health care providers.

To Oversee Compliance with Distribution Restrictions, FDA Relied on Information Submitted by All Drug Sponsors and Its Own Inspections for Some of the Drugs, Including Mifeprex

For all nine of the drugs that have been approved under the restricted distribution provision of Subpart H, FDA has relied mainly on information submitted by sponsors in required reports to oversee the sponsors' compliance with distribution restrictions. For six of the drugs—not including Mifeprex—FDA relied on reports specific to the drugs' restricted distribution programs.[54] The type of information provided by the sponsors in these documents included data on the operation of the restricted distribution program, such as requirements for distributors, pharmacies, prescribers, and patients participating in the program. In addition, to oversee compliance with the restricted distribution programs for most of the drugs—including Mifeprex—FDA has relied on annual reports, supplemental applications, or periodic reports for required updates on the postmarket use of the drugs, including summaries of updates to the restricted distribution program.[55]

Through the end of 2007, FDA had conducted inspections specifically to oversee sponsors' compliance with distribution restrictions for three of the drugs—Mifeprex, Tracleer, and Xyrem. In the case of Mifeprex, in 2002 FDA conducted routine inspections of two of the drug's distributors to oversee their compliance with distribution restrictions. FDA inspectors reviewed standard operating procedures and other information in order to oversee adherence to the requirements of the restricted distribution program such as procedures for maintaining signed provider agreements, distributing medication guides with shipments of the drug, and maintaining the physical security of the drug. For one of the inspections of Mifeprex distributors, FDA did not issue a citation. For the other inspection, FDA issued a citation in which the agency cited four

[54]FDA approved six of the nine Subpart H restricted drugs with a requirement that the sponsor report periodically to FDA specifically on implementation of the respective restricted distribution program. Under FDAAA, sponsors of all drugs with an approved REMS will be required to submit periodically to FDA an assessment of their REMS. Pub. L. No. 110-85, § 901(b), 823 Stat. 929, 932, *codified at* 21 U.S.C. § 355-1.

[55]Though FDA's Subpart H regulations provide an expedited process for withdrawing marketing approval for a drug if FDA determines that promotional materials are false or misleading, the agency has not done so for a Subpart H drug. See 21 C.F.R. § 314.530(a)(5) (2007). However, it has issued warning letters citing the sponsors for two of the drugs—Thalomid and Tracleer—for promoting unapproved use of the drug in violation of FDA regulations.

inconsistencies between the approved distribution plan and the distributor's standard operating procedures. For example, FDA cited the distributor for the absence of certain written procedures pertaining to the distribution of the drug. The sponsor responded to this citation, noting that at the time of approval the distribution plan did not require that distributors prepare such written procedures. Other examples of the inconsistencies FDA noted were serial numbers that had not been properly recorded on a shipping label as required for tracking purposes and the requirement that a medication guide be provided with each dose of the drug was not reflected in the written procedures for processing orders. As a result of its 2006 inspection of the Tracleer restricted distribution program, FDA did not issue a formal citation, but provided recommendations to the sponsor. In its 2007 inspection of the Xyrem restricted distribution program, FDA did not identify any specific deficiencies.[56] However, many of the responsibilities for the program are contracted out to a pharmacy, which was not inspected. The inspection report notes that, for that reason, FDA could not verify whether the sponsor had fulfilled the requirements for the drug's restricted distribution program.

Although FDA's inspections for Mifeprex and Tracleer led to recommendations for improving the respective restricted distribution programs, through the end of 2007, FDA had not conducted inspections of compliance with restricted distribution requirements for six Subpart H restricted drugs. FDA officials told us that the agency has conducted

[56]FDA's inspection report notes that the sponsor refused to provide FDA access to full reports from audits that the sponsor had conducted to evaluate its contractors' compliance with agreed upon responsibilities under the restricted distribution program.

inspections of compliance with distribution restrictions for three additional drugs since the beginning of 2008.[57, 58]

To Oversee Compliance with Postmarketing Study Commitments, FDA Relied on Sponsors' Data That Found That Most Have Unfulfilled Commitments

For the eight Subpart H restricted drugs approved with postmarketing study commitments, FDA has relied on sponsors' annual reports for updates on the status of each commitment. FDA's reviews of these reports are the basis for its determination of the status of each commitment as fulfilled, submitted, pending, ongoing, delayed, released, or terminated. FDA officials told us that the status of postmarketing study commitments for Subpart H drugs is monitored the same way as those commitments for other drugs.

Seven of the eight Subpart H restricted drugs approved with postmarketing study commitments had at least one commitment that was not fulfilled as of September 2007.[59] Of these seven drugs, most have study commitments that FDA has classified as ongoing, pending, or delayed.[60] In the case of Mifeprex, FDA had categorized both of the drug's postmarketing study commitments—to which the sponsor agreed at time of the drug's approval in 2000—as ongoing until December 2007 when the agency changed the status of one of the commitments to released. For the first commitment—a study to compare outcomes for patients whose

[57]In 2008, FDA conducted initial inspections specific to the restricted distribution programs for Accutane, Actiq, and Revlimid. In addition, FDA conducted a second such inspection for the Tracleer program. As of May 13, 2008, the results from these inspections were not available.

[58]In February 2007, agency officials told us that they were working to establish a process to conduct regular inspections to oversee sponsors' compliance with distribution restrictions for Subpart H restricted drugs. Since that time, agency officials told us that FDA had decided to combine the inspection of restricted distribution programs with inspections examining compliance with adverse event reporting requirements. However, agency officials noted in May 2008 that FDA is reevaluating its process for conducting inspections in light of recent legislative changes. Under FDAAA, FDA is required to evaluate, at least annually, for one or more drugs that have elements to assure safe use as part of their REMS, whether those elements assure the safe use of the drug, are not unduly burdensome on patient access, and to the extent practicable minimize the burden on the health care delivery system. 21 U.S.C. § 355-1(f)(5)(B).

[59]FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarket study commitments and has submitted the final report for the third and final commitment.

[60]In its June 2006 report on FDA's management of postmarket studies, the Department of Health and Human Services Office of the Inspector General found that it is common across all drugs approved by FDA with postmarket study commitments for sponsors to have unfulfilled commitments.

health care providers perform a surgical abortion with outcomes for patients who are referred to another facility for follow-up care in the event of treatment failure—the sponsor has reported difficulty in enrolling participants into the study. FDA told us that according to the sponsor, the "vast majority of prescribers" can provide surgical abortion services on site. FDA has opted not to terminate the study, and has categorized it as ongoing. FDA officials told us that this gives the agency additional flexibility in the event that provider or practice patterns change over time, making enrollment of study participants more feasible. The sponsor also has reported enrollment challenges in the case of the second study commitment for Mifeprex—to conduct surveillance of ongoing pregnancies following failure of treatment. FDA officials told us that postmarket experience with the drug has shown that most patients opt to have a surgical abortion in the event that the Mifeprex regimen is not successful in terminating the pregnancy. In December 2007, FDA released the sponsor from this commitment because it determined that the study will no longer provide helpful information because of low enrollment.

FDA has worked with some of the sponsors of the Subpart H restricted drugs to make adjustments to agreed upon commitments that have not been completed.[61] FDA officials told us that the agency has in some cases made changes to a sponsor's postmarketing study commitments or requested new commitments in addition to those specified at approval. For example, FDA recommended several additional postmarketing study commitments for Thalomid following the agency's approval of an expanded indication for the drug. In the case of Tracleer, FDA recommended changes to some of the drug's study commitments. FDA had not requested additions or changes to the postmarketing study commitments for Mifeprex until the agency released the sponsor from its commitment to conduct surveillance of ongoing pregnancies following failure of treatment.

[61]FDA may withdraw approval of a drug approved under Subpart H if a sponsor does not carry out its required postmarketing studies with due diligence. 21 C.F.R. § 314.530(a)(2) (2007). According to FDA, the regulations only require postmarketing study commitments for drugs approved under the surrogate endpoint provision (21 C.F.R. § 314.510) and not for drugs approved under the restricted distribution provision (21 C.F.R. § 314.520). FDAAA provides FDA with additional authority with regard to requiring postmarketing studies and/or trials. See 21 U.S.C. § 355(o)(3).

To Oversee Compliance with Adverse Event Reporting Requirements, FDA Reviewed Sponsors' Data, Conducted Inspections and Identified Deficiencies for Most of the Drugs

To oversee compliance with adverse event reporting requirements, FDA has both reviewed data submitted by sponsors in required reports and conducted inspections. Sponsor reporting for the drugs has included annual reports in which the sponsor provided a summary of the adverse events reported in the previous year; periodic update reports which inform FDA of adverse events monthly, quarterly, or at some other interval established by FDA; and 15-day alert reports for events that are both serious and unexpected. In addition, in some cases sponsors have agreed or FDA has required them to provide 15-day alert reports for other types of serious adverse events. For example, the sponsor of Mifeprex agreed to provide 15-day alert reports for cases of serious infection and ruptured ectopic pregnancy in women who used the drug, and FDA required the sponsor of Thalomid to report suspected or confirmed pregnancy in women taking that drug.[62] In some cases, including for Mifeprex, FDA specifically documented its assessments of adverse event reporting contained in annual, periodic update, or 15-day alert reports or reports submitted to the AERS database. FDA officials told us that staff review all submitted reports, but do not always document their reviews.

In addition to relying on reports submitted by the sponsors, FDA has conducted inspections specifically to oversee the sponsors' compliance with adverse event reporting requirements for eight of the nine drugs, including Mifeprex.[63] Between 2001 and May 2008, FDA had conducted 19 such inspections with a range of none to four inspections conducted for each drug.[64] In the case of Mifeprex, FDA has conducted three inspections—in 2002, 2004, and 2006—related to adverse event reporting. In these inspections, FDA reviewed a variety of documents pertaining to adverse event reporting for Mifeprex, including standard operating procedures, product labeling, MedWatch reporting forms, 15-day alert

[62]Mifeprex labeling specifically cautions against the use of the drug in women with ectopic pregnancy. The sponsor has noted that the condition is not an adverse drug experience as FDA defines the term.

[63]As of May 2008 FDA had not conducted an adverse event reporting inspection for the sponsor of Revlimid since this drug was approved under Subpart H. The agency inspected Celgene—the sponsor of Revlimid and Thalomid—in 2001, 2002, 2004, and 2005, but these inspections occurred before Revlimid was approved in December 2005. FDA officials told us they did not have specific goals for how frequently sponsors are inspected to monitor compliance with adverse event reporting requirements.

[64]These inspections include two inspections of the sponsor of Accutane (isotretinoin). FDA conducted an additional four adverse event reporting inspections of sponsors or the manufacturer of generic isotretinoin products.

reports, complaint file, periodic update reports on adverse events, and annual NDA reports. In addition, FDA documented reviews of samples of the sponsor's adverse event reports for completeness, accuracy, and timeliness.

As a result of the Mifeprex inspections, FDA issued citations for deficiencies related to the accuracy, completeness, or timeliness of some reports as well as for the sponsor's failure to follow certain procedures for handling some adverse event follow-up activities. In each of the Mifeprex inspections, FDA identified some examples of misclassified reports—events which FDA said should have been submitted as 15-day alert reports rather than in periodic reports. For example, FDA cited the sponsor for not classifying some events resulting in hospitalization as serious events and thus not reporting those events as 15-day alert reports. In another inspection, FDA found that some of the sponsor's procedures for reporting and following up on adverse events were inadequate or had not been developed. These deficiencies were similar to those FDA found for other drugs, and FDA identified fewer problematic reports for Mifeprex than for some of the other Subpart H restricted drugs. Following each of the inspections for Mifeprex, the sponsor provided a written response to FDA in which it either agreed to address FDA's findings or noted its disagreement with the deficiencies FDA cited. For example, following the first inspection, the sponsor agreed to address the examples of misclassified or incomplete reporting FDA cited and to reinforce procedures for handling adverse event-related correspondence with its staff. In some cases the sponsor disagreed with FDA's characterization of a deficiency or presented evidence to refute a claim that it had not complied with a reporting requirement or procedure.

As a result of FDA's inspections for the other seven drugs, the agency issued written citations to six of the sponsors for deficiencies. In addition, FDA noted only "oral observations" for the other sponsor. Similar to the Mifeprex inspections, FDA staff reviewed information such as sponsor documentation and standard operating procedures related to adverse event reporting for the other seven drugs for which it conducted inspections. As it did for the Mifeprex inspections, FDA reviewed samples of adverse event reports for completeness, accuracy, or timeliness for most of the other drugs. As it did with Mifeprex, FDA cited some sponsors for deficiencies such as incomplete or late reporting of adverse events or failure to adhere to certain procedures for reporting. For example, FDA cited the sponsor of Thalomid for failure to submit several reports of serious and unexpected adverse events as a 15-day alert report and for late reporting of some other adverse events that included deaths and

hospitalizations. In addition, FDA issued an untitled letter to the sponsor citing its failure to review and submit 82 reports of serious and unexpected adverse events within the required time frame.

FDA was not always consistent in how it documented deficiencies in adverse event reporting. In some of its inspections FDA documented the same type of deficiency as a citation while in others it noted them as oral observations or discussion points. For example, FDA did not issue a citation for the sponsor of Tracleer after inspectors noted 52 late 15-day reports—instead discussing the late reports with the sponsor at the close of the inspection. However, in its first inspection of the sponsor for Mifeprex, FDA issued a citation for failure to file a single 15-day report within the required 15 days. FDA also cited the sponsor for 6 late 15-day reports in each of its two subsequent inspections, although the sponsor refuted this finding in written responses following each inspection. As in the case of Mifeprex, sponsors responded to FDA in writing to describe actions they had taken to address deficiencies or to disagree with FDA's conclusions following an inspection.

To Oversee Postmarket Safety, FDA Used Similar Methods to Review Reported Adverse Events and Took a Variety of Actions in Response to Emerging Concerns

FDA has used similar methods to oversee postmarket safety—monitoring, investigating, and taking action on emerging safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. For Mifeprex, FDA has routinely reviewed the available information on reported adverse events from sources such as annual reports, periodic update reports, 15-day alerts, and data from its AERS database. Since the time Mifeprex was approved, FDA has documented regular reviews and summarized the available data on adverse event reports to monitor the drug's safety. FDA believes that, because the distribution system for Mifeprex requires that prescribing physicians agree to report hospitalizations and other serious adverse events, it is unlikely there are significant numbers of these events that are not reported to FDA. However, FDA acknowledges that because the reporting system is voluntary, the agency cannot be certain that they have reports of all serious adverse events.

FDA officials have concluded that, with the exception of the cases of fatal infection, the reported serious adverse events associated with Mifeprex have been within or below the ranges expected based upon the medical literature on adverse events following medical abortion. In its May 2006

response to congressional inquiries regarding Mifeprex,[65] FDA stated that the most commonly reported serious adverse events had been blood loss requiring a transfusion, infection, and ectopic pregnancy. FDA estimated that 0.023 percent of U.S. women who had taken Mifeprex have required transfusion, compared to a transfusion rate of 0.15 percent observed in international studies of the drug. FDA also noted that the rate of ectopic pregnancy among U.S. women who had used Mifeprex was 0.005 percent, compared to the overall rate of 1.3 to 2 percent in all U.S. pregnancies. Based on the medical literature, FDA estimated that fewer than 1 percent of patients will develop an infection of any kind following medical abortion with Mifeprex.

According to FDA, as of May 2008, among the estimated 915,000 U.S. women who had taken Mifeprex for termination of pregnancy since its approval, the agency was aware of seven deaths that may be related to the use of the drug.[66] Six of the deaths were due to severe infection, and one death involved an undiagnosed ectopic pregnancy. Of the cases involving infection, five of the women were infected with a rare bacterium, *Clostridium sordellii*, while one woman was infected with the bacterium *Clostridium perfringens*. With assistance from the Centers for Disease Control and Prevention (CDC) and other outside experts, FDA has investigated all reported infection-related deaths in U.S. women who have taken the Mifeprex regimen for termination of pregnancy. These investigations included requesting the medical records and autopsy reports for each case; evaluating available adverse event data from the United States, the United Kingdom, and the World Health Organization; consulting with scientific experts and health care providers from inside and outside FDA; and microbiological testing to identify the bacterium involved. In addition, FDA evaluated samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths to test for contamination with the bacteria.[67] FDA found that in the six cases of death

[65]FDA statement to the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, May 17, 2006.

[66]In her testimony to Congress on May 17, 2006, Dr. Janet Woodcock stated FDA was aware of five infection-related deaths in U.S. women. In the course of GAO's research for this study, FDA reported that an additional infection-related death occurred in 2007. In her testimony, Dr. Woodcock also discussed three other cases of deaths in U.S. women who had taken Mifeprex that, following investigation, were determined unlikely to be related to the use of the drug. In addition, she discussed three women in other countries whose deaths were related to the use of mifepristone and misoprostol for medical abortion.

[67]The product tracking provision of the restricted distribution program for Mifeprex enabled FDA to locate the lot numbers for the drugs administered in each of the cases.

due to infection, the women used a regimen of Mifeprex and misoprostol that has not been approved by FDA.[68] FDA has stated that it is aware that many health care providers use modified regimens, and while some of the regimens have been described in the medical literature, FDA has not evaluated the safety and effectiveness of any other regimen than the one described in the drug's approved labeling.

To further explore the nature of the infections, FDA initiated an interagency scientific workshop in May 2006 with CDC and the National Institutes of Health entitled "Emerging Clostridial Disease." These agencies had observed a general increase in the United States in reports of serious clostridial infections including infections in women who had used Mifeprex, that raised questions about *Clostridium's* relationship to fatal illness and pregnancy. According to the meeting minutes, participants discussed recent cases of clostridial infection—including those occurring among women who had taken Mifeprex and misoprostol for termination of pregnancy and those who had not—reviewed what was currently known about these infections, and discussed how to conduct surveillance to ensure that cases and trends of clostridial infections are monitored. At the workshop, a CDC official reported on the history of clostridial infections, including a cluster of ten fatal cases reported in the literature between 1977 and 2001 among previously healthy women. Of the ten cases, eight of the women became infected following childbirth, one became infected following a medical abortion, and the other case was unrelated to pregnancy.

As a result of its investigative efforts, FDA has concluded that the evidence does not indicate that Mifeprex caused the fatal infections. In response to congressional inquiry, FDA stated that "the nature of the relationship between taking a single dose of the drug and the reported cases of serious infection with a rare bacterium is highly uncertain."[69] Laboratory testing of samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths due to infection has

[68]In the case of five of the deaths in the U.S. due to infection, the women used an oral dose of Mifeprex, followed by a dose of misoprostol taken intravaginally. In the other case of death due to infection, the woman used an oral dose of Mifeprex followed by a dose of misoprostol taken by inserting it in the pouch of the cheek. The regimen approved by FDA calls for swallowing doses of both Mifeprex and misoprostol.

[69]See FDA letter to Representative Mark E. Souder, then-Chairman of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, U.S. House of Representatives, July 31, 2006.

shown no evidence of contamination with the bacteria.[70] FDA officials have said that the relationship between the infections and the use of unapproved regimens of Mifeprex and misoprostol remains unknown. Some research has suggested that the use of Mifeprex may suppress the immune system which could lead to infection. However, FDA has noted that if this were the case, the agency would expect to see a higher rate of other types of serious infections in patients who had used the drug, which has not been the case. FDA has noted that findings by the CDC and in the medical literature suggest that pregnancy itself—rather than the medication—may be the critical risk factor for women who have become infected with *Clostridium sordellii*.

FDA, working with the drug's sponsor, has taken a variety of steps—such as issuing warnings and making changes to the product labeling—to address safety concerns for Mifeprex that were identified through postmarket monitoring and investigation. For example, in response to reports of ruptured ectopic pregnancy, FDA developed a questions and answers document about the condition and worked with the drug's sponsor to alert health care providers and to highlight the importance of careful screening for the condition. In addition, FDA approved a labeling change to provide information about the importance of evaluating patients for ectopic pregnancy. In response to concerns about serious infections and associated deaths—all of which involved an off-label use of the drug—FDA issued Public Health Advisories to notify healthcare providers about patient deaths and the treatment regimens used in those cases, and to remind them of the regimen FDA has approved, and that FDA has not established the safety of alternative regimens. In addition, FDA issued a news release, reviewed letters from the sponsor to health care providers and emergency room directors to alert them to the safety concerns regarding serious infection, and approved changes to product labeling including revisions to the warning to include information about the deaths due to serious infection.[71] FDA also has established a Web site with information about Mifeprex, questions and answers about the drug, and

[70]FDA officials told us that the agency did not test for bacterial contamination of the specific lot associated with the most recent death because examination of the prior lots revealed no contamination.

[71]FDA officials told us that the sponsor distributed a letter to all health care providers who had signed the prescriber's agreement as of the time of the distribution of the letter and distributed a letter to all emergency room directors in the United States.

links to other safety-related information.[72] FDA used labeling changes—including updating the medication guide that prescribers agree to discuss with their patients—and information posted on its Web site to remind consumers and health care providers that FDA has not assessed the safety and efficacy of any regimen other than the one approved for the drug and indicated in its labeling.

FDA has similarly monitored adverse events for the other Subpart H restricted drugs. As FDA has done with Mifeprex, the agency has documented periodic safety reviews of the available information it had on reported adverse events for all of the other drugs. FDA's reviews analyzed data on reported adverse events from sources such as annual NDA reporting, periodic update reports, 15-day alerts, and data from the AERS database. Some FDA reviews summarized the available data on a specific type of adverse event—like liver toxicity, or severe bleeding—or adverse events in general, in order to determine whether the data suggest an emerging safety concern for the drug. In addition, in some cases, as it did with Mifeprex, FDA has sought the advice and assistance of other federal agencies and outside experts to investigate serious adverse events.

As a result of its monitoring activities, FDA has identified postmarket safety concerns for most of the Subpart H restricted drugs and has taken similar actions to address them. When FDA has found safety concerns related to a Subpart H restricted drug, it has worked with the drug's sponsor to employ a variety of measures to ensure the drug's safe use. These have included adding or strengthening a warning on the label, issuing a Public Health Advisory, and sending letters to health care providers to alert them to a safety risk. FDA has approved safety-related labeling changes, such as boxed warnings, for eight of the nine drugs. In the case of four of the drugs, including Mifeprex, the agency issued a Public Health Advisory or Safety Alert. The sponsors of five of the drugs including Mifeprex sent a letter to health care providers who prescribe (or may prescribe) the drug to alert them of safety concerns or to communicate new information regarding the drug. For example, in the case of Tracleer, adverse event reports revealed an increased risk of liver damage in patients who were treated with the drug. As a result, FDA and the sponsor notified health care providers of the risk by issuing a Safety Alert, highlighting the need for continued monitoring of liver function in

[72]FDA's Web site for Mifeprex safety information is located at: http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm

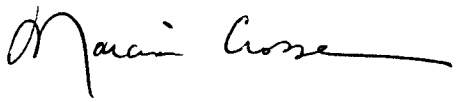
patients using the drug. The sponsor added a boxed warning about potential liver injury to the labeling and issued a letter to health care providers to alert them to the potential risk. In general, the actions FDA took in response to safety concerns were similar across all of the drugs.

Agency Comments

We provided HHS with a draft of this report for review. HHS informed us that it did not have general comments on the draft report. In addition, HHS provided technical comments, which we incorporated as appropriate.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to others who are interested and make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



Marcia Crosse
Director, Health Care

Appendix I: Select Drugs Approved by FDA with Restricted Distribution

Drugs approved under the restricted distribution provision of Subpart H	Condition treated	Application type (year first approved under Subpart H)
Accutane (isotretinoin)	Severe recalcitrant nodular acne.	Supplemental NDA (2005)
Actiq (oral transmucosal fentanyl citrate)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy.	NDA (1998)
Lotronex (alosetron hydrochloride)	Severe diarrhea predominant irritable bowel syndrome (IBS) in women who have: chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and failed to respond to conventional therapy.	Supplemental NDA (2002)
Mifeprex (mifepristone)	Medical termination of intrauterine pregnancy through 49 days' pregnancy.	NDA (2000)
Plenaxis (abarelix for injectable suspension)	Palliative treatment of men with advanced symptomatic prostate cancer, with specified risks or symptoms.	NDA (2003)
Revlimid (lenalidomide)	Treatment of a limited subset of patients with transfusion dependent anemia.	NDA (2005)
	Treatment of multiple myeloma patients who have received at least one prior therapy.	Supplemental NDA
Thalomid (thalidomide)	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.	NDA (1998)
	Newly diagnosed multiple myeloma.	Two Supplemental NDAs[a]
Tracleer (bosentan)	Pulmonary arterial hypertension.	NDA (2001)
Xyrem (sodium oxybate)	Cataplexy associated with narcolepsy.	NDA (2002)
Select Drugs with restricted distribution imposed outside of Subpart H		**Application type (year first approved)**
Clozaril (clozapine)	Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.	NDA (1989)
Tikosyn (dofetilide)	Irregular heartbeats (atrial fibrillation and atrial flutter).	NDA (1999)
Trovan (trovafloxacin/ alatrofloxacin)	Serious, life- or limb-threatening infections in an inpatient healthcare setting.	n/a[b] (1997)

Source: GAO analysis of FDA data.

Note: We list each drug by its trade name with its chemical name in parentheses.

[a]These supplemental NDAs were approved under both the restricted distribution and surrogate endpoint provisions of Subpart H.

[b]Trovan was not originally approved with distribution restrictions. Based on postmarket evidence of serious liver injury in some patients, the sponsor agreed to FDA's requests to limit the distribution of Trovan to patients with specific symptoms only in inpatient settings. However, these restrictions were not associated with a supplemental application.

Appendix II: Detailed Description of Distribution Restrictions for Mifeprex

FDA approved Mifeprex with the following specific restrictions on distribution:

- Mifeprex must be provided by or under the supervision of a physician who possesses adequate qualifications and agrees to provide the treatment according to several guidelines. To accomplish this, the system required that prescribing physicians register with an authorized distributor by providing a signed Prescriber's Agreement attesting to the following:
  - Possesses the ability to assess the duration of pregnancy accurately.
  - Possesses the ability to diagnose ectopic pregnancies.
  - Possesses the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
  - Has read and understood the prescribing information about Mifeprex.
  - Will provide each patient with a medication guide and fully explain the procedure to each patient, provide her with a copy of the medication guide and Patient Agreement, give her an opportunity to read and discuss both the medication guide and the Patient Agreement, obtain her signature on the Patient Agreement and sign it as well.
  - Will notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
  - Will report any hospitalization, transfusion or other serious events to the sponsor or its designate.
  - Will record the Mifeprex package serial number in each patient's record.
- Provisions for the physical security of the drug during distribution such as
  - Direct distribution of the drug through select authorized distributors to physicians who have signed the Prescriber's Agreement, which includes providing their medical license number. Distributors are

required to ensure that the physician is registered before distributing the drug.

- Secure manufacturing, receiving, distribution, shipping, and return procedures, including unique serial numbers on packaging and tamper-proof seals.

Appendix III: Prescriber's Agreement for Mifeprex Distribution

The following is the prescriber's agreement at the time of the Mifeprex approval. Under the restricted distribution program for Mifeprex, the agreement is provided—by the sponsor's licensee Danco Laboratories, Inc.—to all providers to be signed and returned before the prescriber can receive any shipments of Mifeprex.

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician 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 are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov.

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Jill Center; Chad Davenport; and Cathy Hamann made key contributions to this report. Julian Klazkin also contributed.

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ATTACHMENT FIVE

Original Investigation

June 24, 2024

Comparison of No-Test Telehealth and In-Person Medication Abortion

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Key Points

Question Is medication abortion provided using no-test eligibility screening and mailing of medications as effective as in-person care with ultrasonography and safe overall?

Findings This prospective, observational study found that medication abortion obtained following no-test telehealth screening and mailing of medications was associated with similar rates of complete abortion compared with in-person care with ultrasonography (94.4% vs 93.3%, respectively) and met the 5% noninferiority margin, with a low prevalence of adverse events.

Meaning The findings suggest that models of medication abortion care that rely on no-test eligibility assessment and mailing medications to patients are an option for individuals considering medication abortion.

Abstract

Importance In the US, access to medication abortion using history-based (no-test) eligibility assessment, including through telehealth and mailing of mifepristone, has grown rapidly. Additional evidence on the effectiveness and safety of these models is needed.

Objective To evaluate whether medication abortion with no-test eligibility assessment and mailing of medications is as effective as in-person care with ultrasonography and safe overall.

Design, Setting, and Participants Prospective, observational study with noninferiority analysis. Sites included 4 abortion-providing organizations in Colorado, Illinois, Maryland, Minnesota, Virginia, and Washington from May 2021 to March 2023. Eligible patients were seeking medication abortion up to and including 70 days' gestation, spoke English or Spanish, and were aged 15 years or older.

Exposure Study groups reflected the model of care selected by the patient and clinicians and included: (1) no-test (telehealth) eligibility assessment and mailing of medications (no-test + mail) (n = 228); (2) no-test eligibility assessment and pickup of medications (no-test + pickup) (n = 119); or (3) in-person with ultrasonography (n = 238).

Main Outcomes and Measures Effectiveness, defined as a complete abortion without the need for repeating the mifepristone and misoprostol regimen or a follow-up procedure, and safety, defined as an abortion-related serious adverse event, including overnight hospital admission, surgery, or blood transfusion. Outcomes were derived from patient surveys and medical records. Primary analysis focused on the comparison of the no-test + mail group with the in-person with ultrasonography group.

Results The mean age of the participants (N = 585) was 27.3 years; most identified as non-Hispanic White (48.6%) or non-Hispanic Black (28.1%). Median (IQR) gestational duration was 45 days (39-53) and comparable between study groups (*P* = .30). Outcome data were available for 91.8% of participants. Overall effectiveness was 94.4% (95% CI, 90.7%-99.2%) in the no-test + mail group and 93.3% (95% CI, 88.3%-98.2%) in the in-person with ultrasonography group in adjusted models (adjusted risk difference, 1.2 [95% CI, −4.1 to 6.4]), meeting the prespecified 5% noninferiority margin. Serious adverse events included overnight hospitalization (n = 4), blood transfusion (n = 2), and emergency surgery (n = 1) and were reported by 1.1% (95% CI, 0.4%-2.4%) of participants, with 3 in the no-test + mail group, 3 in the in-person with ultrasonography group, and none in the no-test + pickup group.

Conclusions and Relevance This prospective, observational study found that medication abortion obtained following no-test telehealth screening and mailing of medications was associated with similar rates of complete abortion compared with in-person care with ultrasonography and met prespecified criteria for noninferiority, with a low prevalence of adverse events.

Introduction

Medication abortion with mifepristone and misoprostol was first approved by the US Food and Drug Administration (FDA) in 2000 and is currently approved for use through 70 days' gestation in pregnancy.[1] In 2023, medication abortion accounted for 63% of abortions in the US, an increase from 53% in 2020 and 31% in 2014.[2-4] Multiple studies have firmly established the safety and effectiveness of the mifepristone and misoprostol regimen for medication abortion; the incidence of major complications or serious adverse events (SAEs) is less than 0.5% and overall effectiveness in ending the pregnancy without the need for a follow-up procedure is 95% to 97%.[5-10]

In recent years, access to various medication abortion models has expanded rapidly, including telehealth or virtual eligibility assessment and counseling, mailing medications directly to patients, and, in some instances, forgoing the requirement for an in-person ultrasonography or physical examination to establish location and duration of pregnancy prior to provision of medication abortion.[11] The FDA's removal of the in-person dispensing requirement for mifepristone, which had long been part of the drug's Risk Evaluation and Mitigation Strategy, facilitated this expansion. Emerging research evaluating the safety and effectiveness of telehealth and in-person, no-test models[12-14] builds on prior evidence demonstrating that provision of medication abortion by telemedicine (with ultrasonography and/or physical examination) has a comparable safety and effectiveness profile to in-person provision.[15-19] A 2022 retrospective cohort study of 2379 pregnant people accessing medication abortion using history-based (no-test) eligibility assessment in the US reported 94.5% effectiveness in ending the pregnancy and rate of SAEs of 0.42%.[20] Similarly, a large, retrospective cohort study of over 50 000 patients receiving medication abortion in the UK reported effectiveness rates of 98% to 99%, with no difference between those accessing care with and without routine pretreatment ultrasonography.[21]

Further evidence on the effectiveness and safety of telehealth and in-person, no-test (without ultrasonography or physical examination) medication abortion informs expansion of these models to all pregnant people seeking abortion, particularly those now living in the 21 states where abortion is banned or heavily restricted[22] or the 6 states where abortion remains legal but telehealth or mailing of medications is banned.[23] The present study compares the effectiveness and safety of medication abortion provided using 2 models of no-test, telehealth abortion care (mailed or pickup medications) with in-person care with ultrasonography.

Methods

This was an observational, prospective study comparing medication abortion effectiveness and safety using different methods of eligibility assessment (ultrasonography vs no-test) and dispensing of medications (mail vs in-person). The study protocol, including the statistical analysis plan, was published at Open Science Framework in April 2022 prior to initiating any analyses.[24]

Participants and Procedures

Participants were recruited from 4 abortion-providing organizations in 6 states (Colorado, Illinois, Maryland, Minnesota, Virginia, and Washington) between May 2021 and March 2023. We selected organizations that offered direct-to-patient telehealth or other no-test, history-based eligibility screening models that could dispense mifepristone using a mail-order pharmacy and, to allow for an appropriate comparison group, that also offered in-person provision at a facility within the same clinic network and state. One organization had facilities in 3 states and offered telehealth services to patients in those same states through a centralized call center. Thus, there were a total of 6 facilities, 1 in each state (eFigure 1 in Supplement 1). Eligibility was restricted to

patients aged 15 years or older (3 facilities) or aged 18 years or older (3 facilities), English or Spanish speakers, seeking and eligible for medication abortion at that facility, and intending to take the medication up to and including 70 days' gestation. Participants were typically approached by facility staff during initial counseling; those interested in participating received a longer description of the study and then completed electronic informed consent and signed a Health Insurance Portability and Accountability Act waiver allowing clinic staff to review the patients' medical records with the study team. Patients then shared contact information for survey follow-up and received a $15 gift card for enrolling.

Data Collection

Study data were obtained from 2 sources. First, participants were asked to complete electronic surveys 1 day, 2 weeks, and 1 month after receiving the medications. Survey links were sent via text or email and included up to 5 reminders. Surveys were designed such that participants with an unclear abortion outcome (eg, who responded "I'm not sure" if the medications worked to end the pregnancy) were sent repeat surveys until an outcome was ascertained or the patient was considered lost to follow-up. Participants were remunerated with gift cards worth $25 for completing the first and third surveys and $15 for completing the second survey.

Clinics abstracted medical record data using a standardized tool[25] 6 weeks after the initial appointment. If care was ongoing, clinics continued to abstract clinical data until the outcome of the abortion was known or adverse events (AEs) had resolved. In-depth, follow-up chart review was conducted for all cases with an unclear abortion outcome or potential AE.

Measures

The primary exposure was model of medication abortion care received. There were 3 groups: (1) no-test (telehealth) eligibility assessment by history and mailing of medications (no-test + mail); (2) no-test eligibility assessment (via telehealth or in-person) by history and pickup of medications (no-test + pickup); or (3) in-person assessment with ultrasonography and in-person dispensing of medications (in-person).

The primary outcome was effectiveness of medication abortion defined as a complete abortion without need for procedural abortion or repeating the mifepristone and misoprostol regimen.[26] We relied on a combination of patient self-report (survey) and clinic (chart-abstracted) data to determine effectiveness. Survey questions included patients' self-assessment of whether they "believe[d] that the abortion pills worked to end the pregnancy," had taken a pregnancy test and its result, "had a suction procedure (vacuum aspiration or dilation and curettage [D&C]) to complete the abortion," or had been "given another dose of the first abortion pill (mifepristone)" as part of follow-up care. Chart-abstracted data included the clinician's assessment of the medication abortion outcome at last contact with the patient (complete, incomplete, ongoing pregnancy, unknown), any tests performed to document pregnancy outcome (ie, ultrasonography, physical examination, review of symptoms, urine pregnancy test,

serum human chorionic gonadotropin testing), and details on any follow-up care received or reported to the clinic. A flowchart was developed a priori to resolve discordant patient self-report and chart-abstracted outcomes (eFigure 2 in Supplement 1). Clinic staff completing abstraction were not blind to the study group because this information was in the patient's medical record.

A secondary outcome was safety, defined as reporting of any abortion-related SAE. This included overnight hospital admission, surgery, blood transfusion, or death. Surveys assessed whether patients had "go[ne] to a hospital, emergency department, doctor's office, or clinic (other than your regularly scheduled follow-up visit)" since taking the mifepristone and, if so, what type of care they received (including "I was given a blood transfusion" or "I stayed overnight in the hospital"). Chart-abstracted data included any documented care received at an outside facility as well as details on the care received. We searched across all chart-abstracted data fields for a list of terms related to the defined SAEs to ensure all potential cases were identified. All open-ended chart data fields were also reviewed by a physician (D.G.) to determine whether an SAE was reported.

We collected sociodemographic and pregnancy characteristics prespecified as potential confounders, including participants' age, race and ethnicity, gestational duration, parity, and prior abortion. Race and ethnicity data were based on 2 prespecified questions regarding Hispanic, Latine, or Spanish ethnicity (yes or no) and self-reported race (Asian, Black or African American, Middle Eastern or North African, Native American or Other Pacific Islander, White, or other), with the option to select all that apply and/or write in a response. Gestational duration at initial appointment collected by facility staff was estimated using date of last menstrual period for the telehealth groups and ultrasonography for the in-person with ultrasonography group. For race and ethnicity, prior abortion, and parity, we relied on participants' survey responses; when possible, missing responses were completed using medical record data.

Statistical Analysis

We described the distribution of sociodemographic and pregnancy covariates in the study sample overall. We then tested for differences in the distribution of these covariates as well as the proportion with abortion outcome data by study group using bivariable mixed effects linear or multinomial regression models adjusted for clustering of observations by facility as well as standardized mean differences. Although our prespecified statistical analysis plan describes adjusting for clustering by *site*, our subsequent inclusion of facilities from the same organization but located in different states led to a preference for adjustment for clustering at the state and facility level, in the spirit of the prespecified plan. However, to ensure robustness of findings, we also included sensitivity analyses with random effects for organization (n = 4).

Among enrolled participants who took mifepristone or misoprostol and had abortion outcome data available, the unadjusted proportion (with 95% CI) with a complete abortion by study group was calculated. For the primary, prespecified analysis, we

examined noninferiority of the telehealth (no-test) with mailed medications care group compared with the in-person care with ultrasonography group. From a logistic mixed effects model with a random effect for facility, we calculated the unadjusted risk difference (and 95% CI) in effectiveness between telehealth (no-test) with mailed medications and in-person care. We then reran the same model with the addition of prespecified confounders, including age and gestational duration, as well as any variables found to differ by study group in bivariable analysis. Telehealth (no-test) with mailed medications care was considered noninferior if the lower side of the 2-sided CI was above −5%, chosen to be consistent with prior research.[27-29] As secondary, prespecified analyses, we then repeated these steps to examine noninferiority of no-test + pickup (vs in-person) and either no-test (vs in-person with ultrasonography) care. We also descriptively examined the proportion (with 95% CI) in each study group that experienced an SAE and, when possible, differences in proportions by study group from adjusted models.

Prespecified analyses focused on a complete-case analysis. However, to ensure robustness of study findings, we repeated our primary, prespecified analysis using multiple imputation by chained equations. We imputed missing data for all covariates and the primary outcome (effectiveness) using all covariates in the original adjusted models as well as receipt of public assistance, educational attainment, and whether they completed a survey. We then used Stata's MI estimate command and a logistic regression model using imputed values and the mimrgns command to estimate the risk difference between study groups (StataCorp). We utilized an inverse probability of treatment-weighted regression adjustment approach to balance covariates between study groups and re-estimate the risk difference. Specifically, logistic regression was used to calculate the propensity score or probability of treatment (telehealth + mail). We then calculated weights as 1/propensity score for the treated group and 1/1-propensity score for the untreated (in-person with ultrasonography) and reran a logistic regression model applying this weight. Finally, to allow for interpretation of marginal, population-level effects, we repeated the primary analysis using a logistic regression model with robust standard errors for facility.

Sample Size

We determined the minimum sample size required to establish noninferiority of telehealth (no-test) with mailed medications care to in-person care for the primary effectiveness outcome. Assuming 20% loss to follow-up, moderate correlation of observations by site (increasing sample size by an additional 15%), and effectiveness of 95%,[7,30] a sample size of 170 participants per study group, or 510 participants overall, gave 80% power with a 1-sided α of .025 to establish noninferiority of telehealth (no-test) with mailed medications care. The study was not powered to detect noninferiority of different models with respect to safety.

All study activities were approved by the University of California San Francisco institutional review board in January 2021 (#20-32514). This manuscript was prepared in accordance with STROBE guidance.[31]

Results

A total of 1107 patients were approached, of whom 878 were eligible; 588 consented and enrolled (Figure). There were no differences in mean age (*P* = .38), appointment type (*P* = .72), or gestational duration (*P* = .51) between those eligible who enrolled vs did not enroll.

Among 588 enrolled patients, 3 were excluded from the analysis because they did not receive (n = 1) or take (n = 1) pills or because they sought emergency care for an ectopic pregnancy *before* picking up the pills (n = 1), resulting in a final sample of 585. Abortion outcome data were available for 537 of 585 (91.8%) of the participants; the proportion with abortion outcome data did not differ by study group (Table 1). Further, there were no differences by sociodemographic and pregnancy characteristics in the proportion missing abortion outcome data (eTable 1 in Supplement 1).

Median (IQR) participant age was 26 years (23-31). Nearly one-half (48.6%) were non-Hispanic White, with fewer non-Hispanic Black (28.1%), non-Hispanic other, or multiple races (12.1%) or Hispanic (9.6%). Approximately 4 in 10 participants reported a prior abortion (42.6%). Median (IQR) gestational duration at screening was 45 days (39-53) and did not differ by study group (*P* = .39). In the no-test + pickup medications study group, two-thirds (66%) completed eligibility assessment virtually and one-third (33%) completed no-test eligibility assessment in-person at a clinic.

Overall, 510 of 537 participants had a complete abortion without a procedure or repeating the mifepristone and misoprostol regimen, for an unadjusted effectiveness rate of 95.0% (95% CI, 92.8%-96.7%). Among the 27 participants classified as having an incomplete abortion, 18 had a follow-up procedure to complete the abortion, 6 reported a positive pregnancy test or uncertainty about whether the pills worked and were then lost to follow-up, 2 had a confirmed or suspected ectopic pregnancy, and 1 reported receiving outside care to complete the abortion to the study clinic. One ectopic pregnancy was confirmed by the patient, who reported to the clinic that they had sought care at an emergency department after taking the medications and had an operation to remove a fallopian tube. The other participant was referred to a hospital for evaluation and treatment of a suspected ectopic pregnancy after reporting no bleeding for more than 24 hours after taking misoprostol.

Unadjusted effectiveness was 94.1% (95% CI, 90.1%-96.8%) in the in-person group, 95.1% (95% CI, 91.2%-97.6%) in the no-test + mail group, and 96.5% (95% CI, 91.2%-99.0%) in the no-test + pickup group. After adjustment for covariates including age, race and ethnicity, and gestational duration, the risk difference between the in-person and no-test + mail groups was 1.2% (95% CI, −4.1% to 6.4%), above the limit of −5% and indicating noninferiority of telehealth (no-test) with mailed medications care. In this adjusted model, effectiveness was 94.4% (95% CI, 89.6%-99.2%) in the no-test + mail group and 93.3% (95% CI, 88.3%-98.2%) in the in-person group. Similarly, the adjusted risk difference between the in-person and no-test + pickup care groups was 1.7% (95% CI, −4.6% to 8.1%), indicating noninferiority of no-test + medications pickup care. In this

adjusted model, effectiveness was 95.0% (95% CI, 88.8%-100.0%) in the no-test + pickup care group and 93.3% (95% CI, 88.8%-97.8%) in the in-person group (Table 2).

In sensitivity analyses, rerunning models with imputed missing observations, with application of inverse probability of treatment weights, and with adjustment for clustering of observations by organization (vs facility), results were consistent and demonstrated noninferiority of the no-test model (eTable 2 in Supplement 1).

Overall, 6 of 537 participants experienced an SAE, for a rate of 1.1% (95% CI, 0.4%-2.4%). Events included 4 overnight hospitalizations, 2 blood transfusions, and 1 surgery (for treatment of ectopic pregnancy). The unadjusted rate of SAEs was 1.5% (95% CI, 0.3%-4.2%) in the telehealth + mail group (n = 3) and 1.4% (95% CI, 0.3%-3.9%) in the in-person group (n = 3); no SAEs were reported in the no-test + pickup care group. In adjusted logistic models with robust standard errors for state, the adjusted risk difference between the in-person with ultrasonography and no-test + mail care group was 0.4 (95% CI, −1.0 to 1.7), indicating noninferiority of the no-test + mail model (eTable 3 in Supplement 1).

Discussion

In this prospective, observational study of 585 people obtaining medication abortion, it was found that medication abortion following no-test telehealth screening and mail-order pharmacy dispensing of medications was associated with similar rates of complete abortion as in-person care with ultrasonography, met the prespecified threshold for noninferiority, and had a low rate of AEs overall. Further, medication abortion following no-test screening with pickup of medications was also associated with similar outcomes as in-person care with ultrasonography and had low rates of AEs overall. Levels of effectiveness with models of care incorporating telehealth and eligibility assessment in this study were comparable to large 2022 and 2024 studies of no-test telehealth patients.[20,32] This study contributes new evidence pertaining to no-test telehealth models in direct comparison with a concurrent control group of people receiving care from similar facilities through in-person care with ultrasonography. Taken together, these findings indicate that no-test and telehealth models with mailing of medications may be offered as an option to people seeking abortion. Although geographic and logistical barriers have always delayed and complicated pregnant people's access to abortion,[33,34] these barriers have become increasingly problematic following the Supreme Court's June 2022 decision revoking federal protections on abortion.[35,36] Thus, expansion of telehealth and no-test or history-based models offers a safe and effective, as well as urgently needed, way to overcome at least some of the logistical and geographic barriers to accessing abortion.[37]

Study findings may also be used to refute ongoing efforts to further regulate and restrict access to medication abortion, most notably in the *Alliance for Hippocratic Medicine v FDA* case currently before the US Supreme Court. One of the central issues being considered in this case is the quality of the evidence the FDA relied on when it removed

the in-person dispensing requirement for mifepristone in 2021.[38] Although the data were robust in 2021 when the FDA performed its review, this current analysis, as well as other research published since then,[20,32] further strengthens the evidence documenting the safety and effectiveness of medication abortion provided using no-test telehealth screening for eligibility and dispensing the medications by mail.

Limitations

This study has limitations. First, approximately 8% of the participants were lost to follow-up and did not complete a survey or have any follow-up contact with the clinic. Although this follow-up rate represents an improvement over prior research that relied only on chart-abstracted outcomes,[12,13,19,20] the possibility that those who were lost to follow-up had worse outcomes remains. Second, only patient-reported outcomes up to 4 weeks after initiation of treatment were collected; it is possible that additional treatment could have been accessed after that point. Third, as an observational study in which patients could select which model of medication abortion care they received, some differences in the sociodemographic and pregnancy characteristics by study group were expected and therefore the study relied on adjustment for these characteristics to account for them in analyses. Reassuringly, differences were not observed in gestational duration by study group, which is likely most strongly correlated with outcomes of safety and effectiveness,[7] and models with imputed data produced comparable findings. However, confounding on unobserved covariates always remains a possibility in observational data. Fourth, this study sample size was not powered to detect noninferiority of, or differences in, safety of different models of care. Although few SAEs (n = 6 [1.1%]), including ectopic pregnancy, were observed, the estimate is qualitatively higher than a large 2022 retrospective study of patients receiving medication abortion through history-based screening, which found that 0.5% experienced an SAE.[20] Inclusion of patient self-reported outcomes, including overnight hospitalization, in defining SAEs likely contributed to this. Notably, the concurrent control group allowed direct comparison of the rate of SAEs between those receiving no-test telehealth medication abortion with mailing of medications vs in-person care with ultrasonography.

Conclusions

This prospective, observational study found that medication abortion following no-test telehealth screening and mailing of medications was associated with similar rates of abortion completion compared with in-person care with ultrasonography, meeting the prespecified threshold for noninferiority and with a low prevalence of adverse events.

Back to top

Article Information

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Author Contributions: Dr Ralph had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ralph, Baba, Biggs, Grossman.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ralph, Baba.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Ralph, Baba, Biggs.

Obtained funding: Grossman.

Administrative, technical, or material support: Ralph, Baba, McNicholas, Hagstrom Miller, Grossman.

Supervision: Grossman.

Conflict of Interest Disclosures: Dr McNicholas reported receiving grants from University of California San Francisco (UCSF) as co-investigator during the conduct of the study and being the Chief Medical Officer for Planned Parenthood of the St. Louis Region. Ms Hagstrom Miller reported receiving grants from UCSF during the conduct of the study. Dr Grossman reported receiving personal fees from The Lawyering Project and Planned Parenthood Federation of America for serving as an expert witness in cases challenging abortion restrictions, including restrictions on telemedicine. No other disclosures were reported.

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ATTACHMENT SIX

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 MIFEPREX 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 she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.
Advise the patient to take the MEDICATION GUIDE with her if she visits an emergency room or another healthcare provider who did not prescribe MIFEPREX, so that provider knows that she is undergoing a medical abortion. (5.1, 5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	3/2016
Indications and Usage (1)	3/2016
Dosage and Administration, Dosing Regimen (2.1)	3/2016
Dosage and Administration, Post-treatment Assessment: Day 7 to 14 (2.3)	3/2016
Warnings and Precautions, MIFEPREX REMS Program (5.3)	3/2016
Warnings and Precautions, Ectopic Pregnancy (5.4)	3/2016

----------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 www.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: 3/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosing Regimen
2.2 Patient Management Following Misoprostol Administration
2.3 Post-treatment Assessment: Day 7 to 14
2.4 Contact for Consultation
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infections and Sepsis
5.2 Uterine Bleeding
5.3 MIFEPREX REMS Program
5.4 Ectopic Pregnancy
5.5 Rhesus Immunization
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)
7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)
7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*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 MIFEPREX 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 she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.

Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

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.

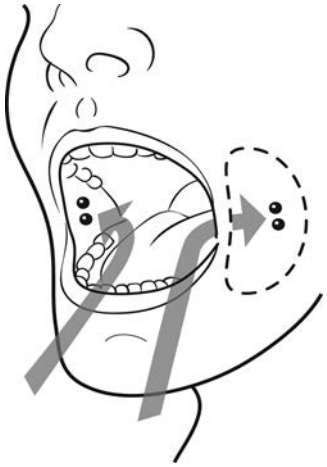
Remove any intrauterine device ("IUD") before treatment with MIFEPREX begins [*see Contraindications (4)*].

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 her to be when she takes 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 she has questions following the administration of the misoprostol

- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, women may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took Mifeprex and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Women who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute renal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute renal insufficiency)

- History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
- Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)
- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX *[see Boxed Warning]*. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. 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. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion *[see Boxed Warning]*.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring

surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

5.3 MIFEPREX REMS Program

MIFEPREX is available only through a restricted program under a REMS called the MIFEPREX REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the MIFEPREX REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form
- Patients must sign a Patient Agreement Form.
- MIFEPREX must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices and hospitals by or under the supervision of a certified prescriber

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)].* Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from US studies, because rates reported in non-US studies were markedly lower and are not likely generalizable to the US population. In three US clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label.

Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most women can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# US studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-US Clinical Studies

Adverse Reaction	US			Non-US		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Mifepristone is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant women are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant women with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformaties were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

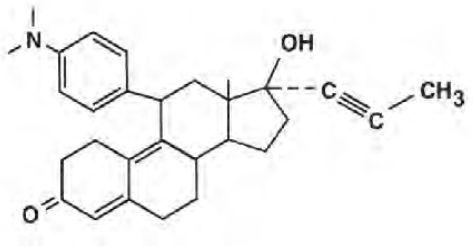
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in women of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	<49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see Warnings and Precautions (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see Warnings and Precautions (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program [see Warnings and Precautions (5.3)]. Under the Mifeprex REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only available in clinics, medical offices and hospitals and not through retail pharmacies.

Provider Contacts and Actions in Case of Complications

- 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, or if she experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
- Advise the patient to take the Medication Guide with her if she visits an emergency room or another healthcare provider who did not prescribe MIFEPREX, so that provider will be aware that the patient is undergoing a medical abortion with MIFEPREX.

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer her to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse.

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3/2016

MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone) tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room. Take this Medication Guide with you. When you visit an emergency room or a healthcare provider who did not give you your Mifeprex, you should give them your Medication Guide so that they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider in a clinic, medical office, or hospital.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.
- Your healthcare provider will either give you or prescribe for you 4 misoprostol tablets to take 24 to 48 hours later.

24 to 48 hours after taking Mifeprex:

- Place 2 misoprostol tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects.These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 3/2016

ATTACHMENT SEVEN

The assessment of blood pressure in pregnant women: pitfalls and novel approaches

Alice Hurrell, MBBS; Louise Webster, PhD; Lucy C. Chappell, PhD; Andrew H. Shennan, MD

Accurate assessment of blood pressure is fundamental to the provision of safe obstetrical care. It is simple, cost effective, and life-saving. Treatments for preeclampsia, including antihypertensive drugs, magnesium sulfate, and delivery, are available in many settings. However, the instigation of appropriate treatment relies on prompt and accurate recognition of hypertension. There are a number of different techniques for blood pressure assessment, including the auscultatory method, automated oscillometric devices, home blood pressure monitoring, ambulatory monitoring, and invasive monitoring. The auscultatory method with a mercury sphygmomanometer and the use of Korotkoff sounds was previously recommended as the gold standard technique. Mercury sphygmomanometers have been withdrawn owing to safety concerns and replaced with aneroid devices, but these are particularly prone to calibration errors and regular calibration is imperative to ensure accuracy. Automated oscillometric devices are straightforward to use, but the physiological changes in healthy pregnancy and pathologic changes in preeclampsia may affect the accuracy of a device and monitors must be validated. Validation protocols classify pregnant women as a "special population," and protocols must include 15 women in each category of normotensive pregnancy, hypertensive pregnancy, and preeclampsia. In addition to a scarcity of devices validated for pregnancy and preeclampsia, other pitfalls that cause inaccuracy include the lack of training and poor technique. Blood pressure assessment can be affected by maternal position, inappropriate cuff size, conversation, caffeine, smoking, and irregular heart rate. For home blood pressure monitoring, appropriate instruction should be given on how to use the device.

The classification of hypertension and hypertensive disorders of pregnancy has recently been revised. These are classified as preeclampsia, transient gestational hypertension, gestational hypertension, white-coat hypertension, masked hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia. Blood pressure varies across gestation and by ethnicity, but gestation-specific thresholds have not been adopted. Hypertension is defined as a sustained systolic blood pressure of $\geq$140 mm Hg or a sustained diastolic blood pressure of $\geq$90 mm Hg. In some guidelines, the threshold of diagnosis depends on the setting in which blood pressure measurement is taken, with a threshold of 140/90 mm Hg in a healthcare setting, 135/85 mm Hg at home, or a 24-hour average blood pressure on ambulatory monitoring of >126/76 mm Hg. Some differences exist among organizations with respect to the criteria for the diagnosis of preeclampsia and the correct threshold for intervention and target blood pressure once treatment has been instigated. Home blood pressure monitoring is currently a focus for research. Novel technologies, including early warning devices (such as the CRADLE Vital Signs Alert device) and telemedicine, may provide strategies that prompt earlier recognition of abnormal blood pressure and therefore improve management.

The purpose of this review is to provide an update on methods to assess blood pressure in pregnancy and appropriate technique to optimize accuracy. The importance of accurate blood pressure assessment is emphasized with a discussion of preeclampsia prediction and treatment of severe hypertension. Classification of hypertensive disorders and thresholds for treatment will be discussed, including novel developments in the field.

Key words: ambulatory blood pressure, aneroid devices, aspirin, cardiovascular, chronic hypertension, CRADLE VSA, gestational hypertension, home blood pressure, hypotension, masked hypertension, mean arterial pressure, preeclampsia, shock, shock index, telemedicine, validation, vital sign alert device, white-coat hypertension

Introduction

The assessment of blood pressure (BP) is the cornerstone of antenatal, intrapartum, and postnatal care. Accurate measurement of BP enables the diagnosis and management of hypertensive disorders of pregnancy, including chronic hypertension, gestational hypertension, and preeclampsia (PE). Furthermore, measuring BP will identify hypotension, secondary to hemorrhage or septic shock, prompting the instigation of life-saving treatments. Globally, PE, hemorrhage, septic shock, and unregulated termination of pregnancy

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account for >50% of global maternal deaths each year.[1] Treatments for PE, including antihypertensive drugs, magnesium sulfate, and delivery, are available in many settings.[2] If hypertension is promptly and accurately identified and appropriate action taken, maternal deaths can be avoided; in the United Kingdom, there is now <1 maternal death from hypertensive disorders of pregnancy per 1 million births.[3,4]

This review will outline the classification of hypertensive disorders of pregnancy, recommended BP devices in pregnancy, and potential pitfalls and sources of inaccurate measurements. Severe hypertension, thresholds for treatment, and novel developments in the field will be discussed, including early warning alert devices such as the CRADLE Vital Signs Alert (VSA) device and telemedicine.

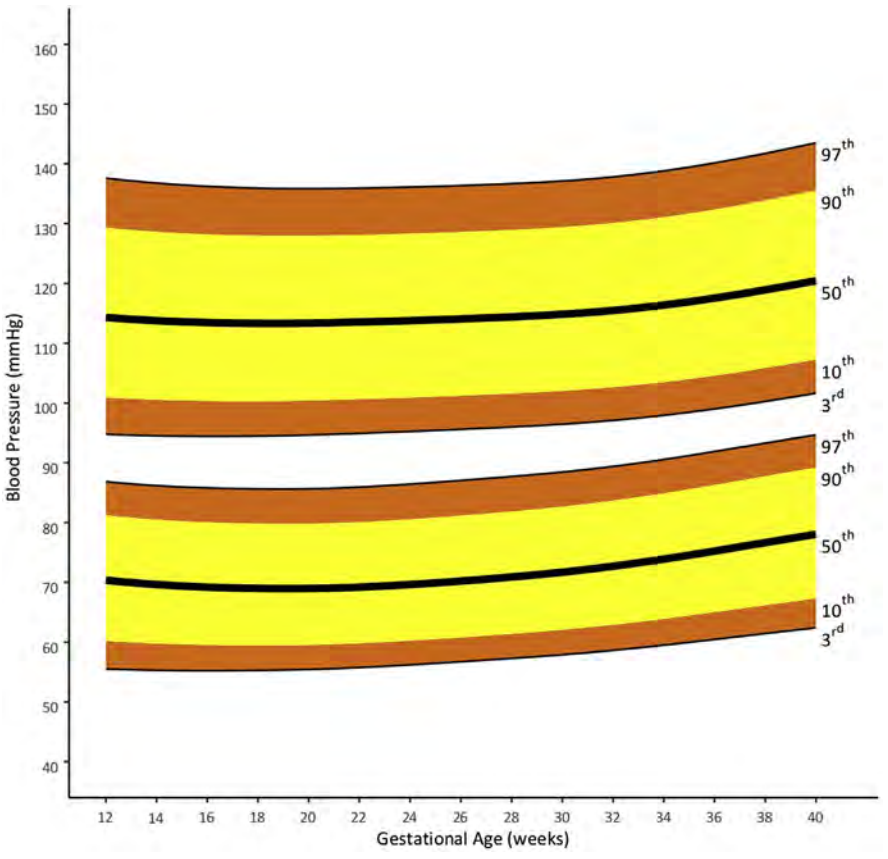
Classification of Hypertensive Disorders in Pregnancy

Hypertension in pregnancy is defined as a sustained (≥2 readings at least 4 hours apart) systolic BP of ≥140 mm Hg or a sustained diastolic BP of ≥90 mm Hg.[5] The International Society for the Study of Hypertension in Pregnancy recommends that the threshold of diagnosis depends on the setting in which the BP measurement is taken, with a threshold of 140 or 90 mm Hg for BP measured in a healthcare setting, 135/85 mm Hg at home, or a 24-hour average BP on ambulatory monitoring of >126/76 mm Hg, in recognition of the "white-coat" phenomenon.[6] Although BP can vary across gestation (Figure 1), gestation-specific thresholds have not been adopted, and a single threshold for healthcare settings is recommended to facilitate the ease of interpretation for healthcare professionals.[7,8] Furthermore, there are differences in BP in different populations. One study of 4023 pregnancies in Asian women found that mean arterial pressure was approximately 4% lower than that in a white population (median multiple of median value of mean arterial pressure, 0.961; 95% confidence interval [CI], 0.956−0.965).[9,10]

Hypertensive disorders of pregnancy are classified as PE, PE with severe features, transient gestational hypertension, gestational hypertension, white-coat hypertension, masked hypertension, chronic hypertension, and chronic hypertension with superimposed PE.[6] Chronic hypertension is defined as hypertension predating the pregnancy or diagnosed before 20 weeks' gestation (Table).[11] Outside of pregnancy, the American College of Cardiology (ACC) and the American Heart Association (AHA) have recently changed their criteria for diagnosing hypertension in adults. BP is classified into 4 categories: normal (systolic BP of <120 mm Hg), elevated (systolic BP of 120−129 mm Hg), stage 1 hypertension (systolic BP of 130−139 mm Hg and diastolic BP of 80−89 mm Hg), and stage 2 hypertension (systolic BP of ≥140 mm Hg and diastolic BP of ≥90 mm Hg).[13] This may lead to an increase in women classified as hypertensive and may result in uncertainties on how to manage women with newly diagnosed stage 1 hypertension when they become pregnant. The American College of Obstetricians and Gynecologists (ACOG) recommends that a conservative approach with a higher level of surveillance is warranted for pregnant women with stage 1 hypertension.[11]

Gestational hypertension is defined as new-onset hypertension in the absence of proteinuria or other features of PE. Very recent evidence suggests that women with stage 1 hypertension according to the ACC and AHA are at an increased risk of adverse pregnancy outcomes.[14] A retrospective single-center cohort study of 2090 women found that women with an elevated BP of 130 to 139/80 to 89 mm Hg after 20 weeks' gestation were at an increased risk

FIGURE 1
BP trajectory changes across gestation



BP, blood pressure.

Hurrell. BP assessment in pregnant women. Am J Obstet Gynecol 2022.

TABLE
The classification of hypertensive disorders of pregnancy, according to different organizations

	American College of Obstetricians and Gynecologists[5,11]	International Society for the Study of Hypertension in Pregnancy[6]	National Institute for Health and Care Excellence[12]
Chronic hypertension	BP of ≥140/≥90 mm Hg, predating the pregnancy or before 20 wk gestation	BP of ≥140/≥90 mm Hg, predating the pregnancy or before 20 wk gestation	BP of ≥140/≥90 mm Hg present at the booking visit or before 20 wk gestation or if the woman is already taking antihypertensive medication when referred to maternity services
Gestational hypertension	New-onset hypertension	New-onset hypertension	New-onset hypertension
	≥140/≥90 mm Hg, after 20 wk gestation, in the absence of features of PE	≥140/≥90 mm Hg, after 20 wk gestation, in the absence of features of PE	≥140/≥90 mm Hg, after 20 wk gestation, without significant proteinuria
PE	New-onset hypertension ≥140/≥90 mm Hg, after 20 wk gestation, with at least one of the following: • Proteinuria (≥ 300 mg per 24-h urine collection or protein-to-creatinine ratio of ≥ 0.3 or a dipstick reading of 2+) • Renal insufficiency (serum creatinine of >1.1 mg/dL or doubling of serum creatinine concentration) • Thrombocytopenia (platelet count of $<100 \times 10^9$/L) • Impaired liver function (elevated liver enzymes to twice the upper limit of normal) • Pulmonary edema • New-onset headache or visual symptoms	New-onset hypertension ≥140/≥90 mm Hg, after 20 wk gestation, with at least one of the following: • Proteinuria (protein-to-creatinine ratio of ≥30 mg/mmol) • Acute kidney injury (creatinine ≥ 90 μmol/L; ≥1 mg/dL) • Hematological complications (platelet count of <150,000/μL, disseminated intravascular coagulopathy, hemolysis) • Liver involvement (elevated transaminase level at >40 IU/L) • Neurologic complications • Uteroplacental complications (fetal growth restriction, stillbirth)	New-onset hypertension ≥140/≥90 mm Hg, after 20 wk gestation, with at least one of the following: • Proteinuria (protein-to-creatinine ratio of ≥30 mg/mmol or albumin-to-creatinine ratio of ≥8 mg/mmol or ≥1 g/L (2+) on dipstick testing) • Renal insufficiency (creatinine of ≥90 μmol/L and ≥1.02 mg/dL) • Hematological complications (platelet count of <150,000/μL, disseminated intravascular coagulopathy, hemolysis) • Liver involvement (elevated transaminase level at >40 IU/L) • Neurologic complications • Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, stillbirth)

BP, blood pressure; *PE*, preeclampsia.

Hurrell. BP assessment in pregnant women. Am J Obstet Gynecol 2022.

FIGURE 2
Devices used to assess BP



A, Mercury sphygmomanometer. **B,** Home BP monitor (Microlife WatchBP Home, image courtesy of Microlife AG). **C,** Home BP monitor (Omron M7 Intelli IT, image courtesy of Omron).

BP, blood pressure.

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of developing hypertensive disorders of pregnancy, with an adjusted risk ratio (RR) of 2.41 (95% CI, 2.02−2.85).[14] The implications of these findings for clinical management require further research to evaluate whether initiation of treatment at stage 1 hypertension thresholds has maternal and fetal benefit (or harm).

PE is defined as new-onset hypertension after 20 weeks' gestation with proteinuria or other evidence of maternal disease, including thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or new-onset headache.[5] New-onset hypertension with fetal growth restriction is classified as PE by the International Society for the Study of Hypertension in Pregnancy, but not by the ACOG.[5,6] Superimposed PE is diagnosed when a woman with chronic hypertension develops evidence of maternal organ dysfunction consistent with PE. Sudden worsening of hypertension or increase in proteinuria should prompt the evaluation for possible superimposed PE, but this may be difficult to diagnose and can be a diagnosis of exclusion.[11] New-onset thrombocytopenia, increase in liver enzymes, elevated uric acid, or sudden development of symptoms should point to the diagnosis of superimposed PE. PE with severe features is defined as severe hypertension (≥160/≥110 mm Hg on 2 occasions at least 4 hours apart), thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, or visual disturbances (hematological and biochemical abnormalities defined by the ACOG provided in the Table).[5]

White-coat hypertension is defined as hypertension in a healthcare setting with normalization of BP of <135/85 mm Hg outside this setting.[6] Masked hypertension describes normotension in a hospital or clinic, with hypertension manifesting in other settings (eg, on home BP readings).[6] The likelihood of progression among classes has been well described, with 15% to 25% of women with gestational hypertension[15] and 25% of women with chronic hypertension progressing to PE.[6] Furthermore, white-coat hypertension is not a benign condition, because 40% of women develop gestational hypertension and 8% develop PE.[16] A recent meta-analysis including 12 studies identified that women with white-coat hypertension have an increased risk of delivering a small-for-gestational-age newborn (RR, 2.47; 95% CI, 1.21−5.05) and preterm birth (RR, 2.86; 95% CI, 1.44−5.68) compared with normotensive women.[17] Therefore, enhanced surveillance may be appropriate for women with white-coat hypertension, and ambulatory or home monitoring may help confirm the diagnosis and guide decisions regarding the initiation of antihypertensive agents.[11]

Blood Pressure Assessment

Auscultatory method

There are numerous methods for assessing BP in pregnant women, including invasive and noninvasive monitoring, with the latter comprising auscultatory and oscillatory methods (Figures 2 and 3[18]). In 1896, Riva-Rocci first described the use of a mercury sphygmomanometer to identify systolic pressure.[19] In 1905, Korotkoff introduced the method of auscultation to determine systolic and diastolic BP. A stethoscope is used to auscultate the sound produced when the blood flows through a partially occluded artery. The origin of the Korotkoff sounds is not fully understood but may originate from the turbulence to blood flow and stretching of the arterial wall (see Figure 4).[20,21] For typical BP measurement by the auscultatory method, a cuff is placed around the upper arm and inflated to 20 to 30 mm Hg above the point where the radial pulse is no longer palpable. The cuff is slowly deflated at approximately 2 mm Hg per second to avoid the underestimation of systolic BP and overestimation of diastolic BP.[19] A stethoscope is placed over the brachial artery in the antecubital fossa (distal to

FIGURE 3
CRADLE Vital Signs Alert device and traffic light warning system



DBP, diastolic blood pressure; *SBP*, systolic blood pressure; *SI*, shock index.
Hurrell. BP assessment in pregnant women. Am J Obstet Gynecol 2022.

the cuff), and the Korotkoff phase 1 (K1) sound, representing the systolic BP, is heard when the pressure in the cuff has deflated sufficiently to allow blood flow through the artery. Korotkoff phases 2 (K2) and 3 (K3) represent a change in the sound quality and can be mistaken for K1 if there is an auscultatory gap, underestimating the systolic BP.[22] This can be identified by palpating the radial pulse, which will be palpable for K2 and K3 and not for K1. The Korotkoff phase 5 (K5) sound is denoted by the disappearance of this sound and represents the diastolic BP. It was previously thought that K5 is a rare occurrence in pregnant women and that Korotkoff phase 4 (K4) (muffling) should be used instead. A randomized trial of the use of K4 or K5 to monitor the BP of 220 pregnant women with hypertension found that K4 was significantly associated with a greater likelihood of recording severe diastolic hypertension (P=.006), but all other episodes of severe hypertension were recorded with similar frequency.[23] In a prospective study of 1460 paired measurements of BP in pregnant and nonpregnant women, Shennan et al[24] demonstrated that K4 showed poor reproducibility, with agreement in only 19% of readings. In contrast, K5 was identified in all measurements, which is significantly more often than K4 (P<.05) and is therefore recommended for use.

The auscultatory method is recognized as the original gold standard for BP measurement. Because most epidemiologic data have been based on this, this remains a reasonable assumption. This was originally performed using a mercury sphygmomanometer but this is no longer recommended owing to the risk of mercury toxicity. Now, mercury sphygmomanometers are only recommended for comparison in monitor validation protocols.[25] Aneroid devices have been developed as the replacement for mercury sphygmomanometers. These devices have an aneroid gauge consisting of a bellows, with a watch-like motion and connected to a compression cuff. Changes in pressure within the system make the bellows expand and contract. This movement rotates a gear, which then turns a pointer across a calibrated dial.[26] However, these are prone to calibration errors, particularly owing to mechanical wear and tear or trauma. Calibration should be performed according to the manufacturer's guidelines; this is usually at least every 2 years.[27] However, recalibration is rarely performed as specified, and 1 study of 279 sphygmomanometers in primary

care found that 53% of aneroid devices read an error of >3 mm Hg compared with 7.8% of combined mercury and automated devices (P=.002).[28] Another study of 1462 sphygmomanometers found that 9.2% gave readings that were >5 mm Hg inaccurate.[29] A study of systematic errors in measurements of BP found that an overestimation of systolic BP by 3 and 5 mm Hg would misclassify 24% and 43% as hypertensive, respectively. An equivalent underestimation would falsely reassure 19% and 30% of patients with systolic hypertension, respectively.[30]

Automated devices

Automated devices use the oscillometric method to measure BP, based on the principle that blood flow through a partially constricted vessel causes the arterial walls to vibrate.[20] The air in the cuff conducts and transfers the vibration to a pressure transducer in the monitor. The pressure at maximum oscillation equates to the mean arterial pressure. Systolic BP is calculated or derived according to changes in the oscillation characteristics in the cuff as it deflates, whereas diastolic BP is often calculated according to an algorithm that incorporates the mean arterial pressure and systolic BP.[19,20] One of the first automated BP monitors, the device for indirect noninvasive automatic mean arterial pressure (Dinamap; Ramsey Medical, Inc., Tampa, FL) was developed in 1976 and is still in frequent use in clinical practice today.

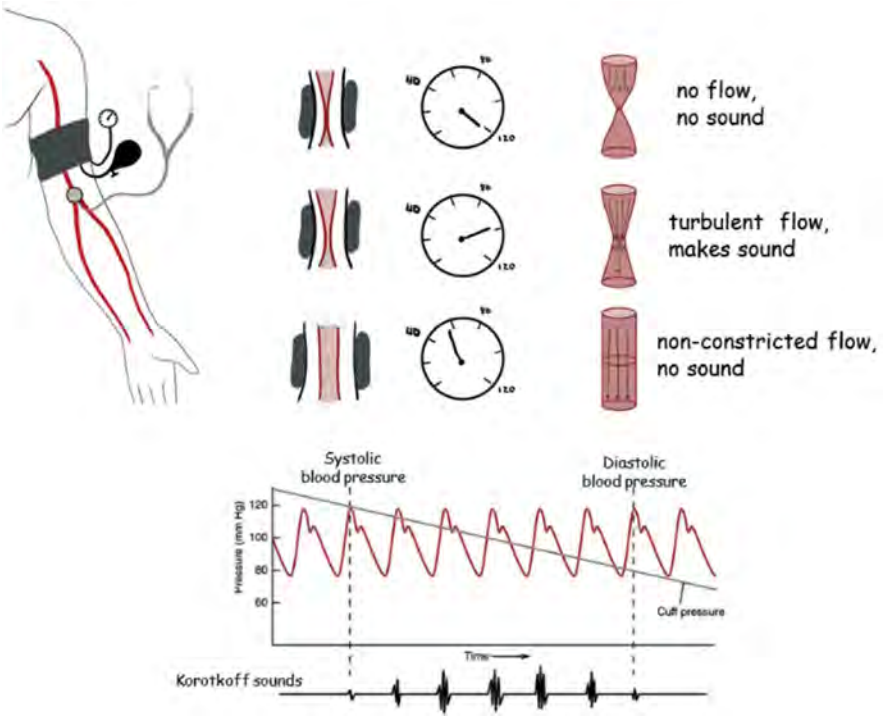
Home blood pressure monitoring

Home BP monitoring, or BP self-monitoring, is when an individual measures their own BP outside of a clinical setting, and this is likely to play an increasingly important role in pregnancy. An advantage of home monitoring is the detection of white-coat and masked hypertension, particularly if ambulatory BP monitoring over 24 hours is not acceptable or available.[20,31] Other potential benefits include reduced face-to-face attendances, enhanced patient convenience, and additional readings providing a better basis for diagnostic and management decisions. The severe acute respiratory syndrome coronavirus 2 pandemic has stimulated numerous maternity units to implement home BP monitoring to reduce face-to-face consultations while maintaining essential monitoring for the mother.[32,33] Trials are underway to evaluate whether home BP monitoring improves the detection of raised BP and reduces systolic BP during high-risk and hypertensive pregnancies.[34] A cohort study of 294 BP measurements from 147 women demonstrated that median systolic BP measurements from home monitoring were lower than clinic measurements (132.0 mm Hg vs 138 mm Hg; P<.001).[35] A feasibility randomized controlled trial of 154 women demonstrated that home monitoring had good acceptability among women and indicated that a larger randomized trial would be feasibile.[36,37] A Cochrane review of settings and technique for monitoring BP during pregnancy concluded that further evidence on self-monitoring of BP is needed, because the only included study was small (n=154).[38] A feasibility randomized controlled trial of self-monitoring in the postnatal period similarly indicated that a larger trial would be feasible and also found that self-management resulted in better diastolic BP control to 6 months.[37] A trial of telemonitoring (incorporating BP monitoring and cardiotocography) is also being conducted to assess the impact on patient safety, satisfaction, and cost effectiveness.[39] The ACOG recommends that ambulatory management at home is an option for women with gestational hypertension or PE without severe features.[5] It is necessary that the BP monitor used is validated in pregnancy and that the woman has been adequately trained on how to self-monitor and escalate, if required. Frequent maternal and fetal surveillance is still necessary, with assessment of proteinuria, hematological and biochemical abnormalities, and ultrasound scans to assess fetal growth.

Ambulatory blood pressure monitoring

Ambulatory BP monitoring involves an individual wearing an ambulatory BP

FIGURE 4
Korotkoff sounds and vessel changes



Hurrell. BP assessment in pregnant women. Am J Obstet Gynecol 2022.

monitor, and BP is automatically measured at repeated intervals through day and night.[40] It is recommended as the definitive test for diagnosing chronic hypertension (outside of pregnancy) in the United States, Canada, and the United Kingdom,[41] because there is evidence of clinical and cost effectiveness.[42–44] However, home BP monitoring may be favored over ambulatory BP monitoring owing to the ease of use with increased availability and lower cost. However, this is a pragmatic decision and there is a balance between a marginal improvement in diagnostic accuracy and clinical utility.[41] Ambulatory BP monitoring has the advantage of identifying nocturnal hypertension, because home BP monitoring is not usually performed at night. This has been particularly associated with deaths and cardiovascular events in the nonpregnant population.[45,46] The diurnal variation in BP is sometimes reversed in pregnant women with PE, with the highest mean arterial pressure seen during the night.[47,48] A study of 24-hour ambulatory BP monitoring in 109 nulliparous women with hypertension after 20 weeks' gestation demonstrated that automated diastolic BP was significantly related to adverse outcomes, including proteinuria (P=.034), preterm delivery (P<.001), birthweight at <10th percentile (P<.001), and admission to the neonatal unit (P=.001), compared with conventional sphygmomanometry in antenatal clinic and an obstetrical day unit.[49] Therefore, ambulatory BP monitoring may have some clinical advantages, but the added difficulty in terms of lower availability and increased cost and inconvenience may not justify its use. The ACOG advises that ambulatory monitoring may be beneficial to guide the diagnosis and treatment decisions in women with white-coat hypertension.[11]

Invasive monitoring

Invasive BP monitoring involves the placement of a cannula into an artery (usually the radial artery) with the external distal end connected to a pressure transducer. Numeric measurements and graphical recordings are presented on a monitor in real time, enabling dynamic management of critically unwell patients in an intensive care setting, including women with severe PE, massive hemorrhage, septic shock, and high-risk cardiac lesions during labor.[20] It is useful for assessing rapid changes in cardiovascular status, rather than identifying diagnostic or treatment thresholds. Validation of oscillometric BP monitors may be against an invasive rather than an auscultatory standard. The risks of invasive monitoring include bleeding, infection, hematoma, embolism of air or thrombotic material, vessel injury, pseudoaneurysm formation, and local nerve injury.[50]

Comparative diagnostic accuracy of devices

Outside of pregnancy, ambulatory BP monitoring is accepted as the best test to diagnose hypertension, because it has been shown to predict cardiovascular events more accurately than other devices.[51] A review of 13 studies comparing 3 diagnostic tests in nonpregnant adults (home BP monitoring with telemonitoring, home BP monitoring without telemonitoring, and clinic BP assessment) with a reference standard of 24-hour ambulatory monitoring found that home BP monitoring without telemonitoring demonstrated the best sensitivity and specificity for identifying hypertension.[51] To the best of our knowledge, there have been few randomized trials comparing the diagnostic accuracy of different modalities of assessing BP in pregnancy. A Cochrane review of settings and technique for monitoring BP during pregnancy has been conducted.[38] This included 3 studies; one was a feasibility study of self-measurement vs clinic measurement,[36] one compared K4 with K5 to represent diastolic BP,[23] and the final trial compared the CRADLE intervention with usual care.[52] Other studies have identified intraindividual variation among types of monitors,[53] and BP is influenced by the environment and the person who is assessing the BP.[54,55] Therefore, further evidence of the diagnostic accuracy of different devices and settings for BP measurement in pregnancy is needed. The most accurate device for assessing severe hypertension in pregnancy has similarly not been established. Many cases of severe hypertension can be appropriately managed without an arterial line.[56]

Calibration

All devices must be calibrated, which relates to whether the pressure transducer equates accurately to a true pressure measured in millimeters of Mercury. A technical calibration check can be performed by an authorized laboratory, which will measure and calibrate the device against a reference manometer, such as an electronic sensor with a high accuracy of ±0.1 mm Hg and standardized to the world pressure standard, or a column of mercury.[57] Devices must be put into a calibration mode to achieve this and checked across the pressure range.

Validated devices in pregnancy

It is paramount that BP monitors are validated in pregnancy. Pregnant women are classified as a "special population" according to BP monitor validation protocols, and validation procedures require at least 15 normotensive pregnant women and at least 15 women with both PE and hypertension.[8,58] Monitors are required to be validated in the general population first in 85 subjects, according to power calculations and consensus agreed by the Association for the Advancement of Medical Instrumentation, the European Society of Hypertension, and the International Organization for Standardization (ISO).[58] In addition to the 85 nonpregnant subjects, 45 pregnant women are further required. The number of additional pregnant women is limited for pragmatic reasons to ensure compliance with validation protocols, including the 15 women in each group.[58]

Validation not only ensures correct calibration but also tests that all aspects of the devices are functioning adequately to achieve a correct BP measurement, including the hardware and the algorithm. The physiological changes in pregnancy include an increase in heart rate and stroke volume, thus increasing cardiac output. Total peripheral resistance is reduced, leading to high capacitance vasculature and a hyperdynamic circulation.[59] Generally, these changes do not interfere with the accuracy of

oscillometric devices, evidenced by devices passing validation studies in normotensive pregnancies, but not pregnancies affected by PE.[60] By contrast, in PE, there is altered vascular reactivity, reduced intravascular volume, and reduced vessel compliance, along with interstitial edema. These changes may affect the amplitude and detection of the oscillometric waveform or alter the validity of the algorithm used to calculate systolic and diastolic BPs.[61] One study compared oscillometric monitoring with invasive monitoring in 6 women with severe PE and demonstrated that the oscillometric monitor significantly underestimated the systolic BP by 19 mm Hg ($P<.01$).[62]

Validation protocols have been agreed by the British Hypertension Society, the European Society of Hypertension, and the Association for the Advancement of Medical Instrumentation, and strict adherence to an individual protocol is fundamental for accuracy and validity.[58] These protocols have now been harmonized into an ISO standard.[58] Of >4000 BP monitors available on the market, few have been evaluated in pregnant women and fewer have passed a validation protocol. In a systematic review of 28 devices examined, 2 ambulatory devices, 2 home devices, 4 clinic BP devices, and 1 home/clinic device passed a validation protocol without any violations.[63] Devices that have been proven valid and accurate should be used, given the consequences of inaccurate BP measurement during pregnancy. The devices that can be recommended for pregnancy are presented in Box 1.

BOX 1

Automated devices validated for use in pregnancy and preeclampsia[a,63,73]

Ambulatory devices	Welch Allyn QuietTrak (Hillrom, Chicago, IL)
	BP Lab (Nizhny Novgorod, Russia)
	PAR Medizintechnik GmbH & Co. Physio-Port (Berlin, Germany)
Clinic devices	Dinamap ProCare 400 (Ramsey Medical, Inc., Tampa, FL)
	A&D UM-101 (A&D Company, Limited, Tokyo, Japan)
	Nissei DS-400 (Nissei, Tokyo, Japan)
	Omron HEM907 (Omron, Kyoto, Japan)
Portable devices	Omron M7 (HEM 780E) (Omron)
	Omron MIT (Omron)
	Omron MIT Elite (Omron)
	Omron HEM-9210T (Omron)
	Omron BP760N (HEM-7320-Z) (Omron)
	Microlife WatchBP Home A (Microlife, Taipei, Taiwan)
	Microlife BP 3BTO-A (Microlife)
	Microlife BP 3AS1-2 (Microlife)
	Microlife WatchBP Home A BT (Microlife)
	Microlife WatchBP Home S (Microlife)
	Microlife CRADLE VSA (Microlife)
	Andon iHealth Track (Andon Health Co. Ltd, Tianjin, China)

BP, blood pressure.

[a]Additional devices may be sanctioned through equivalence criteria. The STRIDE BP website provides an updated list of validated BP monitors.[65]

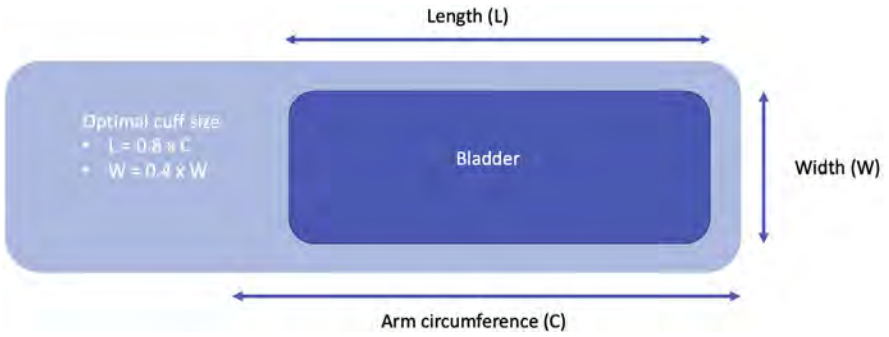
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Technique

BP measurement technique is important and training of healthcare professionals measuring BP is essential but often overlooked. Ideally, for all methods of BP assessment, pregnant women should sit quietly for 5 minutes before assessment. Smoking or ingestion of caffeine or other pressor substances should be avoided for 30 minutes before the assessment.[5] BP measurement should be done sitting or, if this is not possible, in the left lateral position to avoid aortocaval compression. Care should be taken to ensure this latter position does not falsely lower BP by allowing the cuff to rise above the level of the heart.[66] The appropriate cuff size should be selected based on the midarm circumference, which is the midpoint of the line between the olecranon process and the acromion process. An appropriately sized cuff should have a bladder length that is 80% of the arm circumference and width that is 40% of the arm circumference (Figure 5).[19] An inappropriately small cuff will overestimate the BP, enough to misdiagnose hypertension status in 5% to 7% of obese pregnant women.[67] Obesity is increasing and accurate BP assessment in such women is crucial because of the association between obesity and adverse outcomes, as highlighted in reports from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK.[3] Legs should not be crossed, because in 15% of cases, this elevated BP by 2 to 8 mm Hg,[68] and conversation ceased, because this may increase systolic and diastolic BP by as much as 20%.[20] The radial pulse should be palpated, because an irregular heart rate will influence oscillometric accuracy, in which case Korotkoff sounds should then be relied upon.[51]

The FIGO Textbook of Pregnancy Hypertension recommends that if an auscultatory device is used, the first reading should be discarded and an average of the second 2 readings taken, ideally 15 minutes apart. For an automatic device, an average of 2 readings should be reliable.[13,27] Validated devices that automatically measure the BP 3 times and report an average will provide a standardized and unbiased evaluation of BP. Additional technology is available that uses a "weighted" average of at least

FIGURE 5
Blood pressure cuff size



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3 consecutive measurements 15 seconds apart, and 1 study demonstrated that this was a time-efficient equivalent to performing a BP profile over 90 minutes in an obstetrical day unit.[64] It is important to measure BP in both arms at the booking visit and thereafter take BP on the arm with the highest reading. Failure to do so may result in the underestimation of BP in up to a third of cases, and in a study of 5435 pregnant women at 11 to 14 weeks' gestation, the interarm difference in systolic BP was ≥10 mm Hg in 8.3% of women.[69]

There are numerous potential pitfalls and sources of error during this process (Boxes 2 and 3). These can broadly be broken down into manufacturer related, patient related, health system related, and health worker related. Manufacturers must provide appropriately and independently validated devices, with clear limitations and instructions for use. Arm shape may impair BP measurement in morbid obesity, but this can be overcome by specialized cuffs for conical arms.[19] Healthcare settings may have a dearth of validated approved devices or trained professionals to use them. BP monitors must be maintained and calibrated. Finally, healthcare professionals may ask the woman to sit in the wrong position, use poor technique, or perform an insufficient number of measurements (Figure 6). Professionals may exhibit "terminal digit preference," evidenced by 1 study that found 23% of midwives record BP to the nearest 10 mm Hg,[70] and other studies demonstrating that 78% to 85% of BP readings were recorded as ending in a 0.[71,72] Finally, there may be an "observer bias" toward a preferred BP, or "threshold avoidance," to avoid thresholds that require additional work or intervention.[73] Healthcare professionals and providers must strive to overcome these challenges.

Severe Hypertension

BP needs to be measured accurately and frequently in pregnant women to mitigate adverse maternal and perinatal outcomes. Uncontrolled severe hypertension of ≥160/≥110 mm Hg is a risk factor for stroke and as such should be treated as a medical emergency.[74] Prolonged severe hypertension may lead to the loss of autoregulation of the cerebral vasculature, resulting in cerebral hyperperfusion, edema, and disruption of the blood-brain barrier.[20,75,76] However, some evidence suggests that it may be PE that induces a state of abnormal cerebral regulation and that this does not directly correlate with BP.[77] It is recommended that once severe hypertension of ≥160/≥110 mm Hg is detected, first-line treatments are instigated within 30 to 60 minutes to reduce BP.[75] However, there may often be delays in treatment, and delays for >60 minutes have been associated with initial lower BP, absence of PE symptoms, presentation overnight, white ethnicity, symptoms of labor, and increasing gestational age.[78]

In a case series of 28 women who had a stroke owing to severe hypertension, systolic hypertension of >155 mm Hg was seen in all cases immediately before the stroke, whereas only 13% had a diastolic BP of >110 mm Hg.[74] However, there is conflicting evidence, because another study of 30 cases of antenatal stroke demonstrated that the risk of stroke increases by 3% (adjusted odds ratio [OR], 1.03; 95% CI, 1.00−1.05) with a 1 mm Hg rise in systolic BP compared with an 8% increase (adjusted OR, 1.08; 95% CI, 1.03−1.13) with a 1 mm Hg rise in diastolic BP.[79] Posterior reversible encephalopathy syndrome seems to occur at lower systolic BPs in pregnant women compared with the nonpregnant population, necessitating expeditious, controlled reduction of BP. A small study of posterior reversible encephalopathy syndrome found a mean peak systolic BP of 173±17 mm Hg in 13 cases in pregnant women compared with a mean peak systolic BP of 199±54 mm Hg in a study of 113 cases in nonpregnant patients.[80,81] Other short-term complications of severe hypertension include eclampsia, preterm birth, placental abruption, and fetal growth restriction.[63] More recently increased relative risks of future heart failure (RR, 4.19; 95% CI, 2.09−8.38) and cardiovascular disease

BOX 2
Sources of sampling errors

Source of error	Precautions
Rapid deflation	Deflate 2−3 mm Hg/s (deflation duration of >30 s on average)
Auscultatory gap	Obtain systolic pressure by palpation
Threshold avoidance	Check again if in doubt
Digit preference	Record measurement to the nearest 2 mm Hg

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death (RR, 2.21; 95% CI, 1.83−2.66) have been identified.[82]

Risks are not confined to the woman, and hypertensive disorders of pregnancy are associated with 2.6 million stillbirths each year worldwide.[83] PE is a leading cause of iatrogenic preterm birth, with resulting increased perinatal morbidity and mortality, including bronchopulmonary dysplasia, necrotizing enterocolitis, and neurodevelopmental sequelae.[84] The Control of Hypertension in Pregnancy Study (CHIPS) in 987 women found that severe hypertension (≥160/≥110 mm Hg) was significantly associated with the primary study outcome of perinatal loss or high-level neonatal care for >48 hours ($P<.001$).[85] Finally, exposure to a hypertensive pregnancy increases the lifetime risk of hypertension in the infant.[86,87]

Thresholds for Treatment

The thresholds for treatment of hypertension in pregnancy have evolved over time, as new evidence has emerged. Hypertension is classified as BP of 140 to 159/90 to 109 mm Hg and ≥160/≥110 mm Hg as severe hypertension.[11] Until recently, treatment for mild hypertension was not recommended and concern prevailed about the risk of fetal growth restriction if diastolic BP was consistently <85 mm Hg.[88] However, recent evidence from the CHIPS, which compared less tight (target diastolic BP 100 mm Hg) vs tight (target diastolic BP 85 mm Hg) control of hypertension in 987 women with chronic hypertension and gestational hypertension, found that tight BP control reduced the risk of maternal severe hypertension, without increasing perinatal adverse outcomes.[89] This has been incorporated into national guidance in the United Kingdom and Canada, recommending treatment if mild hypertension is sustained.[11,90] The American guidelines have not incorporated this, concluding "tight control of hypertension conferred no benefit to the fetus and had only marginal effects for the woman, namely reduced frequency of progression to severe hypertension."[11] The Chronic Hypertension and Pregnancy trial is ongoing, in which women are randomized to antihypertensive therapy if the BP is >140/90 mm Hg compared with no antihypertensive therapy unless severe hypertension is >160/110 mm Hg thresholds (ClinicalTrials.gov NCT02299414). The results of this trial will further inform guidelines regarding treatment thresholds. The use of mean arterial pressure in the assessment of BP is not recommended, and there is no role for an incremental rise of BP in the absence of persistent hypertension.[11,91]

BOX 3
Sources of oscillometric inaccuracy

Algorithm
Movement
Observer errors (cuff size, level of arm in relation to the heart)
High pressures (≥160/110 mm Hg)
Arrhythmias
Heart valve disease (eg, mitral regurgitation)
Arterial disease (eg, Raynaud syndrome)

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Intrapartum and Postnatal Blood Pressure Assessment

In addition to antenatal BP management, monitoring BP is also critical during labor. Contractions force blood flow from the uterine vessels into the systemic circulation, resulting in increased stroke volume, cardiac output, and BP. Therefore, regular assessment of BP is necessary to safeguard against stroke, eclampsia, and cardiac failure. Measuring BP also facilitates the management of hemorrhage, by assessing the extent of hypovolemia, guiding fluid management, uterotonics, blood transfusion, and appropriate level of care, including transfer to a specialist unit.[92,93]

Postnatal assessment of BP is also crucial. The majority of postnatal eclampsia occurs in the first 48 to 72 hours after birth, and cautious management is necessary during this period.[94,95] Guidance from the National Institute for Health and Care Excellence does not dictate the duration of postnatal admission, but rather the requirement for additional monitoring. BP should be measured at least 4 times a day while the

FIGURE 6
Technique for BP assessment



BP, blood pressure.

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woman is an inpatient and then every 1 to 2 days for up to 2 weeks after discharge, until normotension has been achieved without antihypertensive treatment.[11]

Prediction and Prevention of Preeclampsia

Early identification of women at high risk of developing hypertensive disorders of pregnancy enables prophylaxis with aspirin, as recommended by national guidelines.[3,11] A Cochrane review of 77 studies (including 40,249 women) investigating antiplatelet agents for the prevention of PE found that aspirin reduced proteinuric PE by 18% (RR, 0.82; 95% CI, 0.77−0.88), with a number needed to treat of 61 (95% CI, 45−92).[96] However, a secondary analysis of the Aspirin for Evidence-Based Preeclampsia Prevention trial found that aspirin may be less effective in preventing preterm PE in women with chronic hypertension.[97] A recent randomized, double-blind, placebo-controlled trial of low-dose (81 mg) aspirin for the prevention of preterm birth in 11,976 women in low- and middle-income countries demonstrated a significant reduction in preterm birth in women with hypertensive disorders (RR, 0.38; 95% CI, 0.17−0.85).[98] Therefore, aspirin is a safe and simple strategy that is likely to have far-reaching benefit.

BP can be used as a risk factor to calculate which women will likely benefit from aspirin use. The United States Preventive Services Task Force recommends screening for PE with BP measurements throughout pregnancy, and both the ACOG and the National Institute for Health and Care Excellence recommend obtaining BP measurements at every antenatal visit.[5,11,66]

BP has been incorporated into algorithms used to predict PE.[99,100] The Fetal Medicine Foundation has developed an algorithm to combine maternal risk factors with mean arterial pressure, uterine artery pulsatility index, and serum placental-derived growth factor. A prospective multicenter study of screening for PE in 8775 singleton pregnancies found that this algorithm detected 100% of PE before 32 weeks' gestation, 75% before 37 weeks' gestation, and 43% beyond 37 weeks' gestation, at a false-positive rate of 10%.[101] This was superior to detection according to National Institute for Health and Care Excellence guidelines, which detected 41%, 39%, and 34%, respectively, at a false-positive rate of 10.2%, or the American College of Obstetrician and Gynecologist guidelines, which detected 95%, 90%, and 89%, at a false-positive rate of 64.2%. The use of prediction algorithms such as these emphasizes the importance of accurate BP assessment. In the future, more sophisticated algorithms may need to incorporating multiple of median formulas of mean arterial pressure, to take account of contributing variables such as gestational age, maternal age, weight, height, ethnicity, history of PE, and presence of chronic hypertension or diabetes mellitus.[102]

Shock Index and Early Warning Scores

Hypovolemic shock can initially be difficult to detect, because the physiological increase in blood volume during pregnancy means that women may compensate in the early stages, before rapidly decompensating. More than 60 years ago, shock index was first suggested as an early indicator of excessive blood loss during gastrointestinal hemorrhage.[103] Shock index is the ratio of heart rate to systolic BP and is the most consistent predictor of adverse maternal outcomes, including death.[104] In a retrospective cohort study of 233 women with postpartum hemorrhage, shock index of >0.9 had 100% sensitivity (95% CI, 73.5−1.00) and 43% specificity (95% CI, 36.8−50.3) for predicting intensive care admission, and a shock index of >1.7 had 25% sensitivity (95% CI, 5.5−57.2) but 97.7% specificity (95% CI, 94.8−99.3) for predicting intensive care admission.[105] A study of 958 women from low- and middle-income settings demonstrated that a shock index of >0.9 prompts referral, >1.4 necessitates urgent intervention, and >1.7 indicates a high chance of adverse outcome.[104]

Modified early warning scores have been widely introduced in obstetrics. Color coding of early warning scores according to a traffic light system facilitates prompt identification of abnormal vital signs and thereby early intervention. This was introduced in the United Kingdom after the Confidential Enquiries report in 2003 to 2005.[106] Although evidence of clinical effectiveness is lacking, the use of early warning scores overcomes some of the human factors involved in delayed escalation of care.[107] The effectiveness of early warning scores is clearly dependent on accurate measurement and documentation and appropriate action.

Early Warning Alert Devices

Novel technologies prompting action may circumvent failure to escalate abnormal BP readings. The Microlife CRADLE Vital Sign Alert (VSA) device (Microlife, Taipei, Taiwan) is a semi-automated device that measures heart rate and BP and calculates shock index (Figure 3). It has been specifically designed for low- and middle-income countries, which bear the burden of global maternal mortality and morbidity. Notably, 99% of maternal deaths occur in low- and middle-income settings, and there is an urgent need for simple, cost-effective, robust, and accurate monitoring.[8] The lifetime risk of maternal death is 1 in 36 pregnancies in Sub-Saharan Africa compared with 1 in 6000 pregnancies in high-income countries.[108] In 2015, an estimated 303,000 women died in pregnancy and childbirth, and more than 50% of maternal deaths were caused by hypertensive disorders of pregnancy, hemorrhage, or sepsis.[1]

The CRADLE VSA device has been validated as accurate outside of pregnancy[109] and in normotensive,[110] hypertensive,[110] and hypotensive[111] women, making it widely applicable. The device meets the World Health Organization requirements for suitability for low- and middle-income countries, in that it is affordable (US $20), robust, easy to use, and portable. It has a dual auscultatory/oscillometric function, does not require calibration, and has low

power requirements (it can be charged from a micro-Universal Serial Bus charger, the same as most international phone chargers).[93] The results are shown on a digital display (avoiding digit preference), and it provides an early warning score traffic light, which is triggered by abnormalities in BP or shock index. Qualitative data from healthcare professionals were unanimously positive for the traffic lights early warning system, and pregnant women unanimously liked the device.[112] In 2019, Vousden et al[52] published a pragmatic, stepped-wedge, cluster-randomized trial of the CRADLE VSA device, in 10 clusters in 8 low- and middle-income countries. The device was introduced in primary (first point of access), secondary (first referral point), and tertiary facilities (specialty referral facilities), and all existing devices for measuring vital signs were removed, unless specific functions were needed (such as repeated automated measures in a high-dependency setting).[18] The introduction of the device in conjunction with an educational package led to an absolute reduction in a composite of maternal mortality and morbidity (comprising maternal death, eclampsia, and hysterectomy) of 8%, from 79.4 per 100,000 deliveries before intervention to 72.8 per 100,000. However, after planned adjustments for variation in event rates within and among clusters, the unexpected degree of variability meant the effect could not be attributed to the device.

Novel Technologies and Future Developments

The future of BP measurement will be linked to other novel technologies. Digital innovation and the development of telemonitoring for BP readings to be reviewed remotely by healthcare professionals will likely play more of a role. A number of application-based systems are already available in the United Kingdom, including BPm-Health, Florence, and Hampton.[32] BPm-Health and Hampton have been specifically designed for pregnant women, but Florence is intended for use in the general population.[113] Women can record their BP on the application, and the telemonitoring system incorporates an algorithm that reminds women to submit readings and alerts them to contact their healthcare professional if their BP is abnormal. Healthcare professionals can review BP measurements on the application but are not usually alerted with abnormal BP readings in real time. This is similar to telemonitoring used in the nonpregnant population.[31] The ACOG recommends frequent BP monitoring in the clinic and at home in the case of poorly controlled BP or elevated risk of PE, and digital monitoring will facilitate this. Small studies have demonstrated the advantages of telemonitoring include fewer hospital visits, better BP control, and cost savings.[114–116] Large randomized controlled trials will guide the widespread introduction of home BP monitoring and telemonitoring, if clinical and cost effectiveness is established.[34,39] The integration of telemonitoring is still a work in progress within obstetrics, but this has been achieved in other fields of medicine. A recent randomized controlled trial of 1182 participants found that self-monitoring with telemonitoring was associated with a reduction in BP at 12 months, with an adjusted mean difference of −4.7 mm Hg (95% CI, −7.0 to −2.4).[31] A study of pooled individual patient data from 4 studies showed self-monitoring with telemonitoring increases the likelihood of antihypertensive intensification (OR, 1.8; 95% CI, 1.2−2.6) and could improve BP control rates at 5 years.[117]

Despite promising advances with biomarkers, Doppler velocimetry, and prediction models, there are currently no screening tests for PE with sufficient clinical and cost effectiveness to have been adopted into widespread clinical practice. Therefore, BP monitoring remains the single most important and frequent screening test worldwide.[2] Furthermore, prompt identification of PE relies fundamentally on the frequency of antenatal care.[4] Therefore, work must continue to overcome the complex challenge of instigating basic antenatal care worldwide to reduce inequality and bring down the persistently unacceptable high level of maternal mortality.

Conclusion

BP assessment in pregnant women is a simple procedure of vital importance. It is fundamental to the safety of pregnant women that BP is measured accurately, with a monitor validated in pregnancy and hypertensive disorders of pregnancy. Abnormal results must be acted upon with appropriate measures. In some countries, such as the United Kingdom, universal screening of BP and risk assessment have driven down deaths related to PE to <1 per 1,000,000 births, and this may be attributed to the implementation of evidence-based guidelines and confidential enquiries of adverse outcomes.[118] However, inequality across the globe is stark and work must continue tirelessly to strive for safe childbirth. Universal provision of accurate BP assessment remains a desirable goal. ■

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