UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA
DURHAM DIVISION

AMY BRYANT, MD, Plaintiff, v. JOSHUA H. STEIN, *et al.*, Defendants, and PHILIP E. BERGER, *et al.*, Intervenors-Defendants.	**Case No. 1:23-cv-00077** **INTERVENOR-DEFENDANTS' SUPPLEMENTAL BRIEF**

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INTRODUCTION

The States have long worked in tandem with the federal Food and Drug Administration to protect American consumers from dangerous drugs. Mifepristone is a drug with known serious risks. For this reason, its FDA approval is subject to minimum safety requirements to ensure safe use. North Carolina has chosen to protect the health and safety of its citizens by enacting additional safety measures above the federal floor set by the FDA. These requirements are consistent with Congress's health and safety objectives.

Yet Plaintiff argues that North Carolina's health and safety laws conflict with federal law. It is uncontested that no provision of federal law expressly preempts the challenged state laws and that nothing prevents Dr. Bryant from complying with both federal and state requirements. She nevertheless argues that the state requirements somehow stand as an obstacle to Congress's health and safety objective because the FDA has chosen not to adopt such requirements. Plaintiff can point to no federal statutory text supporting that argument and this Court should uphold the State's health and safety requirements.

LEGAL STANDARD

At the hearing on the Legislative Leaders' Motion to Dismiss, this Court converted the motion and briefing to cross-motions for summary judgment.[1] "Summary judgment is appropriate when 'there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.'" *Reyes v. Waples Mobile Home Park Ltd. P'ship*, No. 22-1660, 2024 WL 236286, at *3 (4th Cir. Jan. 24, 2024) (quoting Fed. R. Civ. P. 56(a)). All parties agree that there is no genuine dispute of material fact in this case. Tr. of Jan. 17, 2024 Mot. Hr'g 38:12–14, 40:14, 100:24–101:2. This Court should grant judgment to the Legislative Leaders as a matter of law.

[1] Intervenors do not object to holding the converted cross-motions for summary judgment in abeyance pending the Supreme Court's decision in *Food & Drug Admin. v. All. for Hippocratic Med.*, No. 23-235 (U.S.). If Respondents prevail on their challenge to the removal of REMS safeguards even in part, that ruling will narrow the scope of the issues presented here.

ARGUMENT

I. North Carolina's health and safety regulations are not preempted by the Food, Drug, and Cosmetic Act.

Under the Supremacy Clause, "federal law preempts—or bars—claims under state law that either interfere with or are contrary to federal law." *Guthrie v. PHH Mortg. Corp.*, 79 F.4th 328, 336 (4th Cir. 2023). However, a court "must not presume federal law preempts state law," *id.*, especially where, as here, Congress legislates "in a field which the States have traditionally occupied," *Wyeth v. Levine*, 555 U.S. 555, 565 (2009). Instead, "any analysis of preemption begins 'with the basic assumption that Congress did not intend to displace state law.'" *Guthrie*, 79 F.4th at 336.

This presumption against preemption can be overcome where "'state law [] stand[s] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *Id.* at 337.[2] But "[i]mplied preemption analysis

[2] Obstacle preemption is unsupported by the Supremacy Clause and inconsistent with separation of powers principles because it permits the elevation of "abstract and unenacted legislative desires above state law." *See, e.g., Virginia Uranium, Inc. v. Warren*, 139 S. Ct. 1894, 1907–08 (2019) (plurality opinion written by Gorsuch, J., and joined by Thomas, J., and Kavanaugh, J.) While the Fourth Circuit has

does not justify a 'freewheeling judicial inquiry into whether a state statute is in tension with federal objectives.'" *Chamber of Com. of U.S. v. Whiting*, 563 U.S. 582, 607 (2011). On the contrary, Supreme Court "precedents 'establish that a high threshold must be met if a state law is to be preempted for conflicting with the purposes of a federal Act.'" *Id.*

In the Fourth Circuit, "[d]etermining whether a state law 'stands as an obstacle' to federal law is a two-step process." *Guthrie*, 79 F.4th at 338. First, a court must "determine Congress's 'significant objectives' in passing the federal law." *Id.* Second, it must determine "whether the state law stands 'as an obstacle to the accomplishment of a significant federal regulatory objective.'" *Id.* Because North Carolina's health and safety regulations do not stand as an obstacle to Congress's purpose of protecting the health and safety of consumers, the challenged laws are not preempted by the FDCA.

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recognized obstacle preemption, the Legislative Leaders reserve the right to argue the doctrine is unsupported by the Supremacy Clause.

A. Congress passed the FDCA to protect the public health by ensuring that drugs are safe and effective.

In 1938, Congress enacted the Food, Drug, and Cosmetic Act (FDCA) to "protect the public health by ensuring that . . . drugs are safe and effective." 21 U.S.C. § 393(b)(2); *Wyeth*, 555 U.S. at 574 ("Congress enacted the FDCA to bolster consumer protection against harmful products."). But "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Wyeth*, 555 U.S. at 575. In 1962, it "added a saving clause, indicating that a provision of state law would only be invalidated upon a 'direct and positive conflict' with the FDCA." *Id.* at 567. "The 'direct and positive conflict' language . . . simply restates the principle that state law is superseded in cases of an actual conflict with federal law such that 'compliance with both federal and state regulations is a physical impossibility.'" *S. Blasting Servs., Inc. v. Wilkes Cnty.*, 288 F.3d 584, 591 (4th Cir. 2002). "And when Congress enacted an express pre-emption provision for medical devices in 1976, . . . it declined to enact such a provision for prescription drugs." *Wyeth*, 555 U.S. at 567.

In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), which amended the FDCA to subject medications with "serious safety concerns" to additional restrictions. Pub. L. No. 110-85, 121 Stat. 823 (2007). Counsel for Dr. Bryant argued at the hearing that the FDAAA added two additional objectives: minimizing burdens on patient access to dangerous drugs, Tr. 41:1–23, and minimizing burdens on "the healthcare system," Tr. 40:23–24. But the FDAAA's language concerning patient access and burdens "is plainly a limitation on the FDA's *own restrictions* on a drug, rather than a command that the FDA assure access for all patients." *GenBioPro, Inc. v. Sorsaia*, No. CV 3:23-0058, 2023 WL 5490179, at *6 (S.D.W. Va. Aug. 24, 2023). Dr. Bryant's counsel acknowledged as much at the hearing. Tr. 41:24–42:3 ("Now, it's true that this statute is directed to the FDA. It's talking about the burdens of the REMS. It's not—it doesn't say in so many words that state law is preempted.").

Therefore, as another district court in this circuit recently held, "Congress's purpose in directing the FDA to consider burden and access when promulgating REMS with

elements to assure safe use was to ensure that the elements *themselves* would not be unduly burdensome upon patient access," *GenBioPro*, 2023 WL 5490719, at *6, not to give the FDA freewheeling authority to preempt state laws it considers "unduly burdensome."[3] The Supreme Court's decision in *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861 (2000), does not require otherwise. In that case, the Court held that the federal National Traffic and Motor Vehicle Safety Act preempted a state common-law tort action where the auto manufacturer was in compliance with federal regulations. *Id.* at 865. The Court relied on the fact that the relevant federal statute contained both an express preemption clause and a savings clause, which canceled each other out, *id.* at 867–74, and Department of Transportation's statement "that a tort suit such as this one would 'stand as an obstacle to the accomplishment and execution' of [the statute's] objectives," *id.* at 874–75, 882.

[3] Although the *GenBioPro* court ultimately found that West Virginia's telehealth provision was preempted, it did so under impossibility preemption. *Id.* at *11. Plaintiffs here have not raised impossibility preemption.

In contrast, FDA has "long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Wyeth*, 555 U.S. at 579. Indeed, FDA specifically acknowledges on its website that States may impose additional restrictions beyond the mifepristone REMS. Exhibit 3, FDA Q&A on Mifepristone at 11. And again, the FDCA contains an express savings clause. That's why the Attorney General concedes that "state law traditionally 'offers an additional, and important, layer of consumer protection that complements FDA regulation." Defs.' Mem. 3, ECF No. 86.

B. North Carolina's health and safety regulations are not an obstacle to accomplishment of Congress's health and safety objective.

Nothing in the challenged laws conflicts with Congress's (or FDA's) ability to protect the public health by ensuring that drugs are safe and effective. On the contrary, North Carolina imposes additional safeguards above the floor set by the mifepristone REMS.

The *Zogenix* cases, which upheld provisions of state law very much like those challenged here, illustrate the point. In *Zogenix I*, the district court held that the State's

emergency order banning a REMS drug approved by FDA was preempted because it effectively required the drug manufacturer "to return to the FDA and seek approval of a drug different from the one that FDA has already deemed safe." *Zogenix, Inc. v. Patrick* (*Zogenix I*), No. CIV.A. 14-11689-RWZ, 2014 WL 1454696, at *2 (D. Mass. Apr. 15, 2014).

However, in *Zogenix II*, the same court upheld revised regulations which "removed" "the obstacle." *Zogenix, Inc. v. Patrick* (*Zogenix II*), No. CIV.A. 14-11689-RWZ, 2014 WL 4273251, at *3 (D. Mass. Aug. 28, 2014). Those regulations imposed additional requirements—including an assessment of patient risk factors, a discussion of the medication's risks and benefits, a pain management treatment agreement, and a letter of medical necessity—above and beyond FDA requirements. *Zogenix, Inc. v. Baker* (*Zogenix III*), No. CIV.A. 14-11689-RWZ, 2015 WL 1206354, at *2 n. 7 (D. Mass. Mar. 17, 2015). And in *Zogenix III*, the district court applied the motion to dismiss standard accepting as true allegations that certain pharmacy regulations would mean the drug was not stocked by pharmacies at all resulting in an "effective ban" on the REMS drug. *Zogenix III*, 2015 WL 1206354, at *2. These

cases demonstrate that reasonable safety measures above the floor set by REMS are not preempted by the FDCA unless they functionally ban an FDA-approved drug.

Yet neither Dr. Bryant nor the Attorney General argued that the challenged laws prevent the FDA from ensuring that mifepristone is safe and effective. Nor have they argued that the challenged laws effectively ban mifepristone.

Instead, recognizing the broad preemptive effect of Plaintiff Bryant's access-plus-burden-on-provider theory, counsel for the Attorney General suggested at oral argument that "where a requirement has been imposed and then withdrawn, . . . preemption becomes obvious." Tr. 99:24–25. But the Attorney General pointed to no statutory text supporting this theory. And none exists. The FDAAA does not suggest that preemption suddenly obtains when FDA removes a requirement. *See* Tr. 94:13–95:17 (Plaintiff arguing against limiting theory).

Again, the object of the FDCA is to ensure drugs are safe and effective, not to minimize burdens on patient access. And for good reason. If this Court accepts Dr. Bryant's invitation to view the 2007 FDAAA amendments as having expanded the

purpose of the FDCA to "minimiz[e] burden on the healthcare system," as well as "burdens" on providers then any state law that touches upon the medical field will be subject to preemption challenge.

There are currently 67 REMS drugs, a category which includes the highest-risk drugs on the market. Exhibit 7, FDA REMS Public Dashboard. These are drugs like opioids, which States have a legitimate and important interest in making sure are prescribed and distributed safely. Dr. Bryant's theory would mean that States can do virtually nothing at the prescriber level to combat the opioid crisis. Plaintiff's theory would declare unconstitutional laws limiting prescribing authority to as little as three days, *see* Ky. Rev. Stat. Ann. § 218A.205(3)(b); limiting dosages that prescribers can give patients, *see* 12-5 Vt. Code R. § 53; and requiring prescribers to obtain a controlled substances certificate from the State, *see* Ala. Code § 20-2-51; *see also* Exhibit 8, Opioid Regulations: State by State Guide. Many States currently enforce such laws even though the FDA declined to adopt dosage and time limits for prescribing

opioids in 2013. Exhibit 9, Delia Stubbs, *Where experts go to learn about FDA*, FDA Law Blog (2013).

Similarly, North Carolina's laws governing mifepristone are hardly unique. On the contrary, twenty-four other States require a waiting period before prescribing mifepristone.[4] Twenty-one States require the reporting of complications from chemical abortion.[5] Eighteen States require some sort of in-

[4] Ala. Code § 26-23A-4(a)(48 hours); Ariz. Rev. Stat. Ann. § 36-2153(A)(1)(24 hours); Fla. Stat. § 390.0111(3)(a)(1)(24 hours); Ga. Code Ann. § 31-9A-3(1)(24 hours); Idaho Code Ann. § 18-609(4) (24 hours); Ind. Code § 16-34-2-1.1(a)(1)(18 hours); Iowa Code § 146A.1(1) (24 hours); Kan. Stat. Ann. § 65-6716(c)(1) (24 hours); Ky. Rev. Stat. Ann. § 311.7735(1) (24 hours); La. Rev. Stat. Ann. § 40:1061.17(B)(3)(a) (72 hours); Mich. Comp. Laws § 333.17015(3) (24 hours); Miss. Code Ann. § 41-41-33(1)(a) (24 hours); Mo. Rev. Stat. § 188.027(1) (72 hours); Neb. Rev. Stat. § 28-327(1)(24 hours); N.D. Cent. Code § 14-02.1-02 (24 hours); Ohio Rev. Code Ann. § 2317.56(B)(1) (24 hours); 18 Pa. Cons. Stat. § 3205(a)(1) (24 hours); S.C. Code. Ann. § 44-41-330(C) (24 hours); S.D. Codified Laws § 34-23A-56 (72 hours); Tenn. Code Ann. § 39-15-202(d)(1) (48 hours); Tex. Health & Safety Code Ann. § 171.012(a)(4) (24 hours); Utah Code Ann. § 76-7-305(2) (72 hours); W. Va. Code § 16-2I-2(a) (24 hours); Wis. Stat. § 253.10(3)(c)(1) (24 hours).

[5] Ariz. Rev. Stat. Ann. § 36-2162; Ark. Code. Ann. § 20-16-1505; Conn. Agencies Regs. § 19-13-D54(b); Idaho Code Ann. § 39-9504; Ill. Admin. Code tit. 77, § 505.40(b); Ind. Code § 16-34-2-4.7; Ky. Rev. Stat. Ann. § 311.7736(2); La. Rev. Stat. Ann. § 40:1061.11(D); Minn. Stat. § 145.4131(b)(5); Miss. Code Ann. § 41-41-109(1)(b); Mo. Rev. Stat. § 188.052(2); Neb. Rev. Stat. § 28-343; N.D. Cent. Code § 14-02.1-07; Ohio Rev. Code Ann. § 2919.123(C)(1); Okla. Stat.

person visit to the clinic.[6] Seventeen States prevent non-physicians from prescribing mifepristone.[7] And eleven require an ultrasound before a chemical abortion.[8] Many of these

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tit. 63, § 1-756.8(D)-(E); Or. Rev. Stat. § 435.496(2); 18 Pa. Cons. Stat. § 3214(h); S.D. Codified Laws § 34-23A-34(24)(a); Tex. Health & Safety Code Ann. § 171.063(g); Wis. Stat. § 69.186(1)(i); Wyo. Stat. Ann. § 35-6-131(a)(iii).

[6] Ariz. Rev. Stat. Ann. § 36-2153; Ark. Code. Ann. § 20-16-1504(c)(1); Fla. Stat. § 390.0111(3)(a)(1); Ind. Code § 16-34-2-1(a)(1); Ky. Rev. Stat. Ann. § 311.7734(2); La. Rev. Stat. Ann. § 40:1061.11(A); Miss. Code Ann. § 41-41-107(2)-(3); Mo. Rev. Stat. § 188.021(1); Neb. Rev. Stat. § 28-335(2); N.D. Cent. Code § 14-02.1-03.5(5); Ohio Rev. Code Ann. § 2919.124(B); Okla. Stat. tit 63 § 1-729.1; S.C. Code Ann. § 44-41-330(A)(1)(a); S.D. Codified Laws § 34-23A-56; Tenn. Code Ann. § 39-15-202(b); Tex. Health & Safety Code Ann. § 171.063(c)(1); Utah Code Ann. § 76-7-305(3)(a); Wis. Stat. Ann. § 253.105(2).

[7] Ariz. Rev. Stat. Ann. § 36-2160(A); Ark. Code. Ann. § 20-16-1504(a); Fla. Stat. § 390.0111(2); Idaho Code Ann. § 18-608A; Ind. Code § 16-34-2-1(a)(1)(B); Iowa Code § 707.7(4); Ky. Rev. Stat. Ann. § 311.7733; Miss. Code Ann. § 41-41-107(1); Mo. Rev. Stat. § 188.020; Neb. Rev. Stat. § 28-335(1); Nev. Rev. Stat. § 442.250(1)(a); N.D. Cent. Code § 14-02.1-03.5(2); Ohio Rev. Code Ann. § 2919.123(A); 18 Pa. Cons. Stat. § 3204(a); Tex. Health & Safety Code Ann. § 171.063(a)(1); Utah Code Ann. § 76-7-332(2); Wis. Stat. § 253.105(2).

[8] Ala. Code § 26-23A-4(b)(4); Ariz. Rev. Stat. Ann. § 36-2156(A); Ark. Code Ann. § 20-16-602(c)(2)(A); Fla. Stat. § 390.0111(3)(a)(1)(b); Ind. Code § 16-34-2-1.1(a)(5); Iowa Code § 146A.1(1); Ky. Rev. Stat. Ann. § 311.7735(4)(a); La. Rev. Stat. Ann. §§ 40:1061.17(B)(1), 40:1061.10(C)-(D); Miss. Code Ann. § 41-41-34(1)(a); Tenn. Code Ann. § 39-15-215(b)(3); Tex. Health & Safety Code Ann. § 171.063(c)(3).

commonsense safety measures have been in place for decades and yet Dr. Bryant's rationale would eliminate them all.

There's no question that the challenged provisions make abortion drugs safer. Ectopic pregnancies are common, 1 in every 50 pregnancies, and ACOG says that an ultrasound is the best way to diagnose the condition. Exhibit 10, ACOG Practice Bulletin No. 193. FDA concedes that complications and failure rates increase with gestational age. Ex. E to Am. Compl., ECF No. 82-5 at 9. That's why FDA told the Supreme Court that the in-person dispensing and counseling requirement was necessary in August of 2020. Appl. for Stay 4, *Food and Drug Admin. v. Am. Coll. of Obstetricians and Gynecologists*, No. 20A34 (U.S.).

Even under Dr. Bryant's theory of the FDAAA many of the challenged provisions do not conflict with any access-plus-burden-on-prescriber standard. The requirement that providers report adverse events is consistent with the transparency purpose behind the FDAAA, *see* Tr. 8:4-14, does not impede access, and routine reporting requirements can hardly be considered a burden. The 14-day follow-up does not mandate that women return but merely requires prescribers to schedule

an appointment and follow-up. N.C. Gen. Stat. Ann. § 90-21.83B(b). That is hardly an unreasonable or burdensome requirement for a high-risk drug. As for the blood type requirement, FDA itself calls testing to determine whether a woman is RH-negative, and thus subject to serious complications with future pregnancies, the standard of care. Exhibit 11, FDA Mifeprex Label. That Dr. Bryant wants to avoid this requirement does not make it overly burdensome. And avoiding it would make abortion drugs *less* safe.

Dr. Bryant's interpretation of the FDCA would not only call those laws into question but also result in a state-law-free zone around any REMS drug. Because nothing in the FDAAA requires such sweeping results, this Court should grant judgment to the Legislative Leaders.

CONCLUSION

For these reasons, the Legislative Leaders respectfully ask this Court to grant summary judgment to the Legislative Leaders.

RESPECTFULLY SUBMITTED THIS 5th day of February, 2024.

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* This email address must be used in order to effectuate service under Rule 5 of the North Carolina Rules of Civil Procedure.

** Email address to be used for all communications other than service.

*** Special Appearance

CERTIFICATE OF SERVICE

I hereby certify that on February 5, 2024, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record.

s/ Erin M. Hawley
Erin M. Hawley

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing document complies with L.R. 7.3(d) and contains 2,986 words. I also certify that this document uses 13-point Courier New Font and has a top margin of 1.25" on each page in compliance with L.R. 7.1(a).

s/ Erin M. Hawley
Erin M. Hawley

Exhibit 1

SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

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 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 of Mifeprex™.
- Must provide each patient with a Medication Guide and 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 both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must 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.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call [redacted]

Sincerely,

/S/

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Exhibit 2

Immediate Complications After Medical Compared With Surgical Termination of Pregnancy

Maarit Niinimäki, MD, Anneli Pouta, MD, PhD, Aini Bloigu, Mika Gissler, BSc, PhD, Elina Hemminki, MD, PhD, Satu Suhonen, MD, PhD, and Oskari Heikinheimo, MD, PhD

OBJECTIVE: To estimate the immediate adverse events and safety of medical compared with surgical abortion using high-quality registry data.

METHODS: All women in Finland undergoing induced abortion from 2000–2006 with a gestational duration of 63 days or less (n=42,619) were followed up until 42 days postabortion using national health registries. The incidence and risk factors of adverse events after medical (n=22,368) and surgical (n=20,251) abortion were compared. Univariable and multivariable association models were used to analyze the risk of the three main complications (hemorrhage, infection, and incomplete abortion) and surgical (re)evacuation.

RESULTS: The overall incidence of adverse events was fourfold higher in the medical compared with surgical abortion cohort (20.0% compared with 5.6%, *P*<.001). Hemorrhage (15.6% compared with 2.1%, *P*<.001) and incomplete abortion (6.7% compared with 1.6%, *P*<.001) were more common after medical abortion. The rate of surgical (re)evacuation was 5.9% after medical abortion and 1.8% after surgical abortion (*P*<.001). Although rare, injuries requiring operative treatment or operative complications occurred more often with surgical termination of pregnancy (0.6% compared with 0.03%, *P*<.001). No differences were noted in the incidence of infections (1.7% compared with 1.7%, *P*=.85), thromboembolic disease, psychiatric morbidity, or death.

CONCLUSION: Both methods of abortion are generally safe, but medical termination is associated with a higher incidence of adverse events. These observations are relevant when counseling women seeking early abortion.
(Obstet Gynecol 2009;114:795–804)

LEVEL OF EVIDENCE: II

Termination of pregnancy is one of the most common gynecologic procedures. For instance, in the United States, nearly half of pregnancies are unintended,[1] and 22% of all pregnancies (excluding miscarriages) end in termination.[2] Abortion practices have changed dramatically in recent years since the medical method with antiprogestin mifepristone and prostaglandins was introduced. For example, in 2007 in Finland 64%,[3] in Sweden 61%,[4] and in the United Kingdom 35%[5] of all abortions were performed using the medical method. Thus, the safety of induced abortion in general, especially that of the medical method, is of great public health interest.

Most previous studies focused on the short-term complications of induced abortion have been small or have not involved comparison of the two dominant methods of abortion (medical and surgical). In a large, register-based study, 5% of the patients had a complication (bleeding, infection, or (re)evacuation) after surgical abortion during a short-term follow-up period of 2 weeks.[6] In a previous meta-analysis in which medical and surgical termination of pregnancy in the

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Funded by Helsinki University Central Hospital (Drs. Suhonen and Heikinheimo), University Hospital of Oulu (Dr. Niinimäki), and The Finnish Cultural Foundation (Dr. Niinimäki).

The authors thank Matti Kesti for his help with computation.

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Financial Disclosure

Dr. Suhonen has lectured at meetings organized by Schering Plough (Helsinki, Finland). Dr. Heikinheimo has been a paid consultant and lecturer for Bayer Schering Pharma AG (Berlin, Germany) and for Schering-Plough (Helsinki, Finland). He also belongs to both the international and Finnish advisory boards for Bayer Schering Pharma. The other authors did not disclose any potential conflicts of interest.

ISSN: 0029-7844/09

first trimester were compared, no differences in pelvic infection or ongoing pregnancies were noted between the methods. Evidence of different rates of other potential side effects or complications between the two abortion techniques could not be confirmed because the trials included were small.[7]

Only a few randomized controlled trials have been performed to compare success rates and complications between medical and surgical abortion.[8–10] In a previous, partly randomized study, no difference in the number of complications was noted. Although the rate of complete abortion was significantly higher in the surgical group (98% compared with 94%), the surgically treated women had a higher incidence of antibiotic treatment than did those undergoing medical abortion.[8] In another randomized controlled trial, complete abortion without a second procedure occurred in 98% of cases after surgical abortion and in 95% after medical abortion. Moreover, no differences in the rates of major complications were observed.[11]

The purpose of the present study was to compare medical and surgical abortion in regard to the incidence and risk factors of immediate (ie, within 42 days after termination of pregnancy) adverse events and complications in a large nationwide cohort. A nationwide cohort with high-quality data derived from national health registries offers the possibility to estimate extensively the risk of adverse events associated with the two methods of early termination of pregnancy. Using this same cohort, we recently reported that the risk of repeat abortion after medical compared with surgical termination of pregnancy depends on various sociodemographic factors but not on the method of abortion.[12]

MATERIALS AND METHODS

This was a cohort study including all women undergoing termination of pregnancy in Finland between January 1, 2000, and December 31, 2006. According to the current law on induced abortions, women need permission with legal indication for termination of pregnancy, but the legislation is interpreted liberally. The Finnish legislation on induced abortion[13] was summarized in our recent study.[12]

The present study was conducted after receiving approval from the ethics committee of the Northern Ostrobothnia Hospital District. The Ministry of Social Affairs and Health and Statistics Finland gave their permission to use the confidential personal-level data from the registries. The Data Protection Ombudsman was notified regarding the data linkage before the analyses as required by the national data-protection legislation.

All women who underwent induced abortion by either medical or surgical methods at a gestational age of 63 days or less were included. The duration of gestation was limited to 63 days because, during the study period of 2000–2006, medical abortions, for the most part, were performed only up to that time.[14] The time of follow-up after abortion was 42 days (6 weeks). Medical abortion was defined as the use of mifepristone alone or in combination with misoprostol or other prostaglandins. Surgical abortion included induced abortions with dilation and curettage or vacuum aspiration. The participants were divided into two arms of the study according to the primary abortion method. For women having more than one abortion, only the first termination of pregnancy during the study period was included.

The study was based on three national registries: the Abortion Registry,[3] the Care Registry for Health Institutions (later renamed the Hospital Registry)[15] complied by the National Institute for Health and Welfare, and the Cause-of-Death Registry of Statistics Finland.[16] The study participants were selected from the Abortion Registry as described in our previous study,[12] after which the other registries were linked with the cohort.

We linked information on the study participants in the Hospital Registry concerning all hospital-inpatient episodes (all hospitals) and outpatient visits (public hospitals) within 42 days after termination of pregnancy to analyze complications related to induced abortion. All of the diagnoses (based on the International Classification of Diseases [ICD]-10, International Statistical Classification of Diseases and Related Health Problems[17]) and codes for surgical procedures (based on the Nordic Classification of Surgical Procedures[18]) found in the cohort were evaluated to select those considered to be of clinical importance.

Complications were divided into seven categories: 1) hemorrhage (all reported hemorrhages), 2) postabortal infections (pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections, and septicemia), 3) incomplete abortion (surgical [re]evacuation, any reported incomplete abortion), 4) injuries or other reasons for surgical operation (all injuries, cervical laceration, uterine perforation, all surgical interventions during the time of follow-up), 5) thromboembolic disease (pulmonary embolism, deep vein thrombosis), 6) psychiatric morbidity (depression, intoxication, psychoses) and 7) death (death from any cause, pregnancy-related death according to the World Health Organization definition). The classification was based on that reported in the Joint Study of

the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists[19] and modified for the present study.

The Cause-of-Death Register kept by Statistics Finland contains data from death certificates and includes all deaths of Finnish citizens and permanent residents in Finland classified according to ICD-10 codes.[20] All of the early deaths (within 42 days of termination of pregnancy) were classified as direct, indirect, or unrelated. This classification was based on that in an earlier study by Deneux-Tharaux et al.[21]

Differences between the groups were assessed using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Logistic regression analyses were performed to adjust for the differences in background characteristics in the comparisons of medical and surgical abortions. Furthermore, logistic regression was used to identify risk factors for complications. Variables that showed statistically significant associations with complications in univariable analysis were further entered in multivariable analysis. The estimated risks are presented as odds ratios with 95% confidence intervals. The statistical analyses were performed by using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

The total number of women in the cohort was 42,619. Of these, 22,368 had primary medical and 20,251 primary surgical termination of pregnancy. The characteristics of the women in the cohort are presented in Table 1. The women in the medical-abortion cohort were somewhat younger and more often primigravid, nulliparous, and single. The most notable difference between the groups was the shorter duration of gestation in the cohort undergoing medical abortion; surgical abortions in Finland usually are performed after the 6th week of gestation.

The incidence of various adverse events and complications is shown in Table 2. The most common adverse events were hemorrhage and incomplete abortion, both of which were more common in the medical group. The incidence of infection did not differ between the groups. Injuries requiring operation were rare but were more common in the surgical group. No differences between the two groups were noted in the incidence of thromboembolic disease, psychiatric morbidity, or death, partly because the overall incidence of these events was low. All of the deaths were unrelated to pregnancy: suicide (n=3), homicide (n=1), subarachnoid hemorrhage (n=1), and traffic accident (n=1).

When comparing the numbers of women with adverse events or complications, the difference between the two groups was notable: 20% of women in the medical-abortion group and 5.6% of women in the surgical-abortion group had at least one type of adverse event. When looking at the number of complications per patient, there were fewer multiple complications after surgical abortion (Table 2).

We also analyzed the three most common complications in relation to the duration of gestation (Fig. 1). In the medical-abortion cohort, the proportion of women with hemorrhage decreased with advancing duration of gestation; with surgical abortion it increased, albeit not significantly. In both groups, the incidence of infection and incomplete abortion increased with advancing duration of gestation.

Univariable and multivariable analyses were performed concerning the risk factors for three major classes of complications (hemorrhage, infection, and incomplete abortion) and for surgical (re)evacuation, separately for the medical and surgical abortion cohorts (Table 3), and for the whole cohort combined (Fig. 2). In multivariable analysis, the risk of hemorrhage after medical abortion was increased in the age group of 20–24 years, among parous women, among those of lower socioeconomic status, and among those living in densely populated or rural areas. The risk decreased with advancing duration of gestation. After surgical termination of pregnancy, an increased risk of hemorrhage was seen in the age groups of 20–24, 25–29, 30–34, and 35–39 years when compared with women younger than 20 years. A rural type of residence was associated with a decreased risk of hemorrhage.

Multivariable analysis revealed an increased risk of infection after medical abortion in the age group of 20–24 years and with advanced duration of gestation of 50–56 and 57–63 days. After surgical abortion, an increased risk of infection was found in the age group of 20–24 years, with increasing duration of gestation, and among women of lower socioeconomic class. A decreased risk of infection was associated with parity and with women living in densely populated or rural areas.

The risk factors associated with incomplete medical abortion were age of 20–24 years, parity, previous abortion, being single, living in a densely populated or rural area, and advanced duration of gestation. The risk of experiencing incomplete surgical abortion was associated with previous abortion, cohabiting or being single, and with a duration of gestation of 57–63 days.

In multivariable analysis, the risk of bleeding was almost eightfold higher, the risk of incomplete abor-

Table 1. Characteristics of the Participants Included in the Study

	Medical Abortion (n=22,368)	Surgical Abortion (n=20,251)	*P*
Age (y)			
Median (mean)	25.0 (26.3)	26.0 (27.3)	<.001
95% confidence interval	26.2–26.4	27.2–27.4	
Age category (y)			
Younger than 20	5,058 (22.6)	4,352 (21.5)	<.001
20–24	5,665 (25.3)	4,337 (21.4)	
25–29	4,098 (18.3)	3,442 (17.0)	
30–34	3,406 (15.2)	3,393 (16.8)	
35–39	2,934 (13.1)	3,130 (15.5)	
40 or older	1,207 (5.4)	1,596 (7.9)	
Parity			
0	12,819 (57.3)	10,171 (50.2)	<.001
1	3,444 (15.4)	3,384 (16.7)	
2	3,897 (17.4)	4,125 (20.4)	
3 or more	2,207 (9.9)	2,570 (12.7)	
Previous abortions			
0	18,626 (83.3)	15,461 (76.4)	<.001
1	2,856 (12.8)	3,471 (17.1)	
2	664 (3.0)	927 (4.6)	
3 or more	221 (1.0)	390 (1.9)	
Marital status			
Married	4,350 (19.5)	4,718 (23.3)	<.001
Cohabiting	3,592 (16.1)	3,113 (15.4)	
Single	14,394 (64.4)	12,412 (61.3)	
Social status			
Upper white-collar worker	1,595 (7.1)	1,497 (7.4)	<.001
Lower white-collar worker	4,799 (21.5)	4,794 (23.7)	
Blue-collar worker	2,691 (12.0)	3,060 (15.1)	
Student	7,598 (34.0)	5,990 (29.6)	
Other	1,072 (4.8)	1,386 (6.8)	
Unknown	4,613 (20.6)	3,524 (17.4)	
Type of residence			
Urban	16,668 (74.5)	15,118 (74.7)	<.001
Densely populated area	2,788 (12.5)	2,286 (11.3)	
Rural	2,912 (13.0)	2,847 (14.1)	
Indication for abortion			
Social reasons	19,691 (88.0)	17,175 (84.8)	<.001
Age 17 y or younger	1,507 (6.7)	1,459 (7.2)	
Age 40 y or older	754 (3.4)	1,076 (5.3)	
Four children or more	366 (1.6)	457 (2.3)	
Other	50 (0.2)	84 (0.4)	
Duration of gestation (d)			<.001
42 or fewer	6,012 (26.9)	1,895 (9.4)	
43–49	7,355 (32.9)	4,724 (23.3)	
50–56	6,014 (26.9)	7,033 (34.7)	
57–63	2,987 (13.4)	6,599 (32.6)	

Data are n (%) unless otherwise specified.

tion was fivefold higher, and the risk of (re)evacuation was twofold higher after medical abortion compared with surgical abortion. The risk of infection, as derived from univariable analysis, was not associated with the method of abortion.

DISCUSSION

In the present study, we found that the two methods of pregnancy termination (medical and surgical) are generally safe. However, the incidence of the two most common adverse events (hemorrhage and incomplete abortion) were notably higher among women undergoing medical abortion, whereas complications requiring surgical treatment, although rare, were more common after surgical abortion. The rates of postabortal infection and serious morbidity (such as thromboembolic events) did not differ between the two groups. There were no pregnancy-related deaths

Table 2. Incidence of Adverse Events in the Cohort

	Medical Abortion (n=22,368)	Surgical Abortion (n=20,251)	P*	Adjusted OR† (95% CI)
Hemorrhage	3,487 (15.6)	433 (2.1)	<.001	7.93 (7.15–8.81)
Hemorrhage with surgical (re)evacuation	645 (2.9)	173 (0.9)	<.001	
Infection	383 (1.7)	342 (1.7)	.85	1.15 (0.98–1.34)
Infection with surgical (re)evacuation	172 (0.8)	122 (0.6)	.02	
Incomplete abortion	1,495 (6.7)	323 (1.6)	<.001	5.37 (4.49–6.28)
Incomplete abortion with surgical (re)evacuation	1,320 (5.9)	77 (0.4)	<.001	
Injury	6 (0.03)	122 (0.60)	<.001	NA‡
Thromboembolic disease	18 (0.08)	17 (0.08)	.90	NA
Psychiatric morbidity	2 (0.009)	1 (0.005)	.62	NA
Death	2 (0.009)	4 (0.020)	.35	NA
Women with adverse events	4,479 (20.0)	1,127 (5.6)	<.001	4.23 (3.94–4.54)
Surgical (re)evacuation	1,320 (5.9)	363 (1.8)	<.001	3.58 (3.18–4.03)
Number of adverse events per woman				
0	17,889 (80.0)	19,124 (94.4)	<.001	
1	3,624 (16.2)	1,021 (5.0)		
2	796 (3.6)	97 (0.5)		
3	59 (0.26)	9 (0.04)		

OR, odds ratio; CI, confidence interval; NA, not applicable.
Data are n (%) unless otherwise specified.
* Chi-square test for comparison between medical and surgical cohort.
† Surgical cohort as a reference adjusted for age, parity, previous abortion, social status, marital status, type of residence, and duration of gestation.
† Not applicable owing to small number of patients in one or both groups.

in our data. Because medical abortion is being used increasingly in several countries, it is likely to result in an elevated incidence of overall morbidity related to termination of pregnancy.

The present study covers almost all of the induced abortions performed in Finland during the years 2000–2006 and thus is a unique data source regarding even uncommon adverse events. However, the validity of the data is a potential problem in register-based studies such as the present one. In the Registry of Induced Abortions, 95% of the information has been proven to be identical to that in medical records.[22] However, the reliability of diagnoses and interventions can vary, and underreporting or overreporting by physicians cannot be ruled out. In addition, the Hospital Registry, which was used as a data source, contains data concerning hospital care only. Thus, adverse events dealt with outside the public hospital system, especially those treated in primary health care, will have been missed. Moreover, a single patient may have various diagnoses and complications, such as incomplete abortion and bleeding, and thus may have been registered more than once. The participants, however, each had a unique personal identification number, and we were able to eliminate double counting in our study.

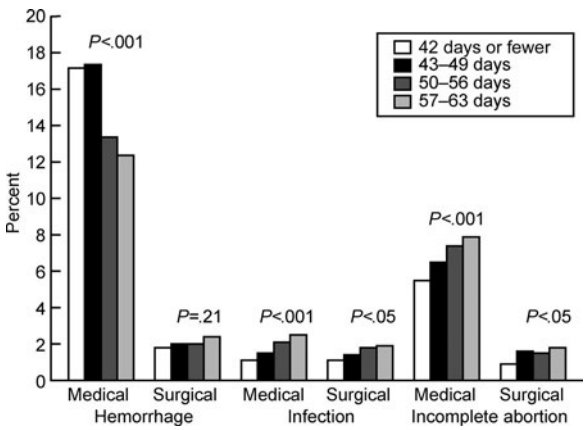

Fig. 1. Complications according to the duration of gestation in the medical and surgical cohorts (%).

Niinimäki. Complications After Medical and Surgical Abortion. Obstet Gynecol 2009.

It is important to note that the severity of the diagnoses found in the Hospital Registry may vary substantially. Thus, another problem in this kind of study is the definition of criteria for complications and adverse events. We evaluated all the ICD-10 diagnoses and codes for surgical procedures included in the Hospital Registry and classified them into seven categories.[19] In addition, women choosing surgical and medical abortion differed subtly in several respects and thus may be prone to different types of adverse events.

The rate of consultation related to a diagnosis of hemorrhage was high and eight times more common after medical termination of pregnancy. Because

Table 3. Results of the Multivariable Analysis in Three Major Complications and Surgical (Re)Evacuation

	Hemorrhage		Infection	
	Medical	Surgical	Medical	Surgical
Age (y)	1.00 (0.96–1.04)			
Age category (y)				
Younger than 20	1	1	1	1
20–24	1.26 (1.00–1.58)	1.72 (1.25–2.37)	1.37 (1.03–1.83)	1.72 (1.13–2.62)
25–29	1.29 (0.88–1.91)	1.82 (1.30–2.54)	1.31 (0.95–1.80)	1.31 (0.77–2.23)
30–34	1.47 (0.83–2.58)	2.01 (1.45–2.79)	0.82 (0.56–1.19)	1.77 (1.02–3.08)
35–39	1.17 (0.56–2.46)	1.79 (1.28–2.52)	1.10 (0.77–1.58)	1.05 (0.54–2.01)
40 or older	1.01 (0.40–2.56)	0.50 (0.26–0.95)	0.95 (0.56–1.61)	1.54 (0.74–3.20)
Parity				
None	1			1
Yes	1.25 (1.08–1.45)			0.80 (0.56–1.14)
Previous abortion				
None	1			
Yes	1.07 (0.93–1.22)			
Social status				
Upper white-collar worker	1			1
Lower white-collar worker	1.14 (0.92–1.40)			3.21 (1.38–7.46)
Blue-collar worker	1.54 (1.23–1.93)			4.40 (1.87–10.36)
Student	1.50 (1.19–1.88)			3.47 (1.44–8.36)
Other	1.58 (1.20–2.08)			4.50 (1.80–11.27)
Marital status				
Married	1			
Cohabiting	1.12 (0.94–1.34)			
Single	1.05 (0.90–1.22)			
Residence				
Urban	1	1		1
Densely populated	1.43 (1.23–1.66)	0.98 (0.72–1.33)		0.85 (0.55–1.32)
Rural	1.25 (1.07–1.45)	0.71 (0.51–0.98)		0.54 (0.33–0.87)
Duration of gestation (d)				
42 or fewer	1		1	1
43–49	0.93 (0.82–1.05)		1.33 (0.98–1.80)	1.03 (.0.59–1.80)
50–56	0.74 (0.64–0.85)		1.91 (1.42–2.56)	1.15 (0.68–1.94)
57–63	0.63 (0.51–0.76)		2.26 (1.62–3.15)	1.15 (0.68–1.96)

Data are odds ratio (95% confidence interval).
Only those variables that showed a statistically significant association with a complication in univariable analysis (data not shown) were entered in multivariable analysis.

medical abortion is associated with uterine bleeding lasting approximately 2 weeks,[23] the high rate of consultation is not surprising. Uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy. The incidence of such bleeding was relatively low, but it was more common in the medical-abortion group. In earlier studies, an average of 10% of women who underwent medical abortion complained of excessive bleeding.[24]

In line with uterine bleeding, the rate of incomplete abortion was higher in the cohort undergoing medical abortion. Surgical evacuation performed because of incomplete abortion occurred in approximately 6% of women having medical termination of pregnancy. The highest rates of complete medical abortion, reported from centers with extensive experience of the technique, are up to 98%.[11,25] However, it is reassuring to note that a high rate of complete abortion, approaching those reported from centers with extensive experience, was reached in the present national cohort.

One of our key findings was that the rates of infectious morbidity were similar after medical and surgical abortion. In a previous survey, the need for postabortal antibiotics for suspected endometritis was higher after surgical abortion.[26] Moreover, the use of medical abortion previously has been associated with rare cases of severe infectious morbidity and mortality.[27] Reassuringly, only two cases with serious infections (septicemia caused by *Staphylococcus aureus* and *Streptococcus*) occurred in the present cohort, one in

Incomplete Abortion		Surgical (Re)Evacuation	
Medical	Surgical	Medical	Surgical
1.04 (0.99–1.10)		1.05 (0.99–1.11)	
1		1	
1.14 (0.80–1.62)		1.15 (0.79–1.67)	
1.05 (0.60–1.86)		1.03 (0.56–1.88)	
0.89 (0.40–2.00)		0.89 (0.38–2.09)	
0.66 (0.23–1.88)		0.66 (0.22–2.00)	
0.41 (0.11–1.52)		0.39 (0.10–1.57)	
1		1	
1.65 (1.33–2.03)		1.59 (1.27–1.98)	
1	1	1	
1.34 (1.11–1.60)	1.38 (1.08–1.76)	1.30 (1.08–1.58)	
1		1	
0.97 (0.75–1.24)		0.97 (0.74–1.28)	
0.83 (0.62–1.11)		0.88 (0.65–1.20)	
1.04 (0.77–1.40)		1.02 (0.74–1.40)	
0.74 (0.50–1.08)		0.84 (0.57–1.25)	
1	1	1	
1.07 (0.84–1.35)	1.46 (1.00–2.13)	1.10 (0.86–1.41)	
0.94 (0.76–1.15)	1.46 (1.09–1.97)	0.92 (0.74–1.14)	
1		1	1
1.40 (1.13–1.74)		1.43 (1.14–1.79)	0.75 (0.52–1.08)
1.38 (1.12–1.70)		1.48 (1.19–1.84)	0.68 (0.48–0.96)
1	1	1	1
0.96 (0.78–1.16)	1.64 (0.97–2.75)	1.01 (0.81–1.24)	1.63 (0.97–2.73)
1.34 (1.12–1.66)	1.59 (0.96–2.62)	1.41 (1.14–1.75)	1.92 (1.17–3.15)
1.55 (1.22–1.98)	1.91 (1.16–3.14)	1.77 (1.38–2.28)	2.23 (1.36–3.65)

the medical and one in the surgical group. However, as previously reported, cases of *Clostridium sordellii* septicemia occurred at a rate of 1 per 100,000[27]; even the present cohort is too small to assess the incidence of such a rare infection.

Injuries and surgical interventions for other reasons were relatively rare in both groups. Not surprisingly, the incidence of postabortal surgical intervention was lower among women undergoing medical abortion. Some other serious and rare complications were identified as well. These included thromboembolic and psychiatric complications as well as some deaths. The incidence of thromboembolic complications is in line with earlier reports of an increased risk during pregnancy.[28,29] In a previous register-based study, it was concluded that deaths from external causes of injury and poisoning (including unintentional and intentional injuries, suicides, and homicides) are significantly more common in women after induced abortion compared with nonpregnant women or women after birth.[30] In the present cohort also, five out of six cases of death were the result of external causes. In addition, psychiatric diagnoses, such as depression and psychoses, were identified, but the rates of these complications did not differ between the two cohorts. Similarly, in an earlier, partly randomized study, no differences between women with medically or surgically performed abortions emerged in regard to postabortal anxiety, depression, or self-esteem.[31] Naturally, the present kind of study setting (register-based study) gives only a crude idea of short-term psychiatric morbidity associated with termination of pregnancy.

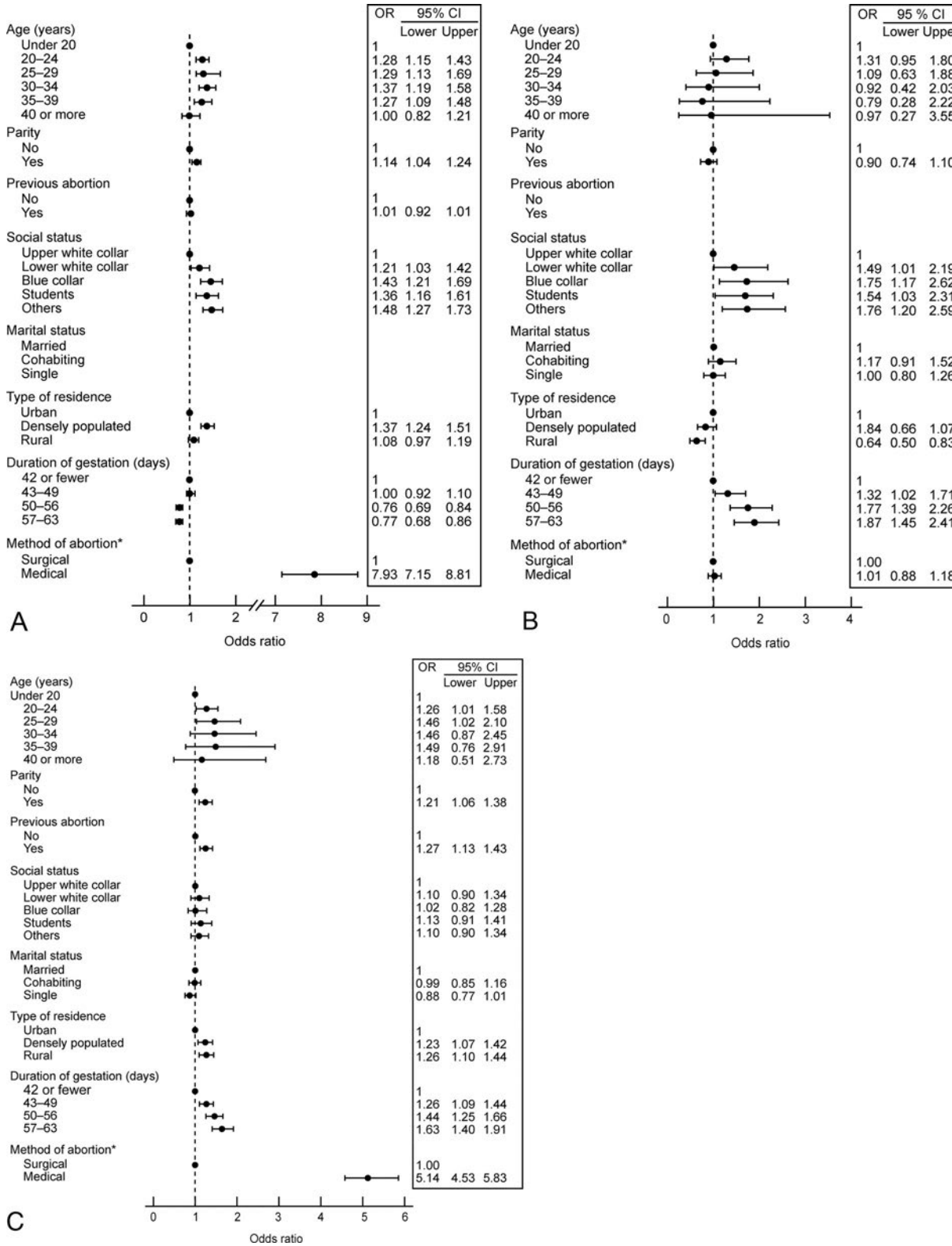

Fig. 2. Risk factors regarding three major complications (bleeding [**A**], infection [**B**], and incomplete abortion [**C**]) among the entire cohort (medical and surgical cohorts combined). OR, odds ratio; CI, confidence interval. *OR for infections is derived from univariable analysis.

Niinimäki. Complications After Medical and Surgical Abortion. Obstet Gynecol 2009.

The most important risk factor with regard to the two most common adverse events (hemorrhage and incomplete abortion) was the method of abortion. Other risk factors were, for the most part, in line with those reported previously–advanced gestational age, parity, and previous induced abortions.[11,32–34] For unknown reasons, the risk of hemorrhage after medical abortion diminished with advancing duration of gestation. Tolerance of bleeding–a natural part of medical abortion–varies from one woman and physician to another and also depends on preabortion counseling. Other explanations, such as possible bias in reporting the events in the registry, are possible but cannot be verified in the present study. We included all cases requiring consultation in specialized health care because they are registered uniformly in Finland. In addition, every such visit adds to the costs of the health care system. More detailed analysis of all health care costs related to termination of pregnancy and its complications, according to the method, is needed.

In conclusion, termination of pregnancy by means of either medical or surgical methods is associated with a low level of serious complications. On the basis of the present data, however, it appears that medical abortion results in an increased incidence of adverse events.

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Exhibit 3

Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation

On this page:

- General Information
- The Mifepristone REMS Program
- Additional Information
- Litigation and Other Legal Issues
- The January 2023 REMS Modification

General Information

1. **What is mifepristone and how does it work?**

   Mifepristone is a drug that blocks a hormone called progesterone that is needed for a pregnancy to continue. Mifepristone, when used together with another medicine called misoprostol, is used to end a pregnancy through ten weeks gestation (70 days or less since the first day of the last menstrual period). The approved mifepristone dosing regimen is:

   - On day one: 200 mg of mifepristone taken by mouth
   - 24 to 48 hours after taking mifepristone: 800 mcg of misoprostol taken buccally (in the cheek pouch), at a location appropriate for the patient
   - About seven to fourteen days after taking mifepristone: follow-up with the health care provider

2. **When did the FDA approve mifepristone for medical termination of pregnancy?**

   The FDA first approved Mifeprex (mifepristone) in September 2000 for medical termination of pregnancy through seven weeks gestation and this was extended to ten weeks gestation in 2016. FDA approved a generic version of Mifeprex, Mifepristone Tablets, 200 mg, in April 2019. The agency's approval of this generic reflects the FDA's determination that Mifepristone Tablets, 200 mg, is therapeutically equivalent to Mifeprex and can be safely substituted for Mifeprex. Like Mifeprex, the approved generic product is indicated for the medical termination of intrauterine pregnancy through 70 days gestation. The labeling for the approved generic version of Mifeprex is consistent with the labeling for Mifeprex.

3. **Who should not take mifepristone, in a regimen with misoprostol, for medical termination of pregnancy?**

An individual should not take mifepristone, in a regimen with misoprostol, for medical termination of pregnancy if it has been more than 70 days since the first day of their last menstrual period, or if they:

- have an ectopic pregnancy (a pregnancy outside of the uterus)
- have problems with the adrenal glands (the glands near the kidneys)
- are currently being treated with long-term corticosteroid therapy (medications)
- have had an allergic reaction to mifepristone, misoprostol or similar drugs
- have bleeding problems or are taking anticoagulant (blood thinning) drug products
- have inherited porphyria (a rare disorder that can affect the liver and other organs)
- have an intrauterine device (IUD) in place (it must be removed before taking mifepristone)

4. **Is it safe to use mifepristone?**

   Yes. Mifepristone is safe when used as indicated and directed and consistent with the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program. The FDA approved Mifeprex more than 20 years ago based on a thorough and comprehensive review of the scientific evidence presented and determined that it was safe and effective for its indicated use. As of 2016, it can be used for medical termination of pregnancy up to 70 days of gestation. The FDA's periodic reviews of the postmarketing data for Mifeprex and its approved generic have not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation. As with all drugs, the FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

5. **What are the possible side effects of using mifepristone for medical termination of pregnancy through ten weeks gestation?**

   The possible side effects are described in the Adverse Reactions section of the labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf) and in the Medication Guide (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf#page=16) for mifepristone.

6. **What serious adverse events have been reported after the use of mifepristone for medical termination of pregnancy through ten weeks gestation?**

   As with all approved drugs, when the FDA receives new information regarding adverse events, the agency reviews the new information and, as appropriate, takes necessary action. This could include, for example, providing updates to health care providers and their patients so that they have information on how to use a drug safely.

   It is common for the FDA to receive reports of serious adverse events for prescription drugs after they are approved. Many drugs are associated with serious adverse events that are known at the time of approval and considered when the FDA makes its approval decision. The FDA

continuously reviews reports of adverse events to, among other things, determine whether they are known risks or whether they are signals of emerging safety concerns.

The FDA has received reports of serious adverse events in patients who took mifepristone. As of December 31, 2022, there were 32 reports of deaths in patients associated with mifepristone since the product was approved in September 2000, including two cases of ectopic pregnancy (a pregnancy located outside the womb, such as in the fallopian tubes) resulting in death; and several fatal cases of severe systemic infection (also called sepsis). The adverse events cannot with certainty be causally attributed to mifepristone because of concurrent use of other drugs, other medical or surgical treatments, co-existing medical conditions, and information gaps about patient health status and clinical management of the patient. A summary report of adverse events that reflects data through December 31, 2022, is here (/media/164331/download?attachment). The FDA has reviewed this information and did not identify any new safety signals. The FDA intends to update this summary report as appropriate.

7. **What should health care providers watch for in patients who have taken mifepristone for medical termination of pregnancy through ten weeks gestation?**

   Health care providers should review the approved labeling for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg. The signs and symptoms they should watch for are included in the labeling, available here (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf).

8. **What is an ectopic pregnancy?**

   An ectopic pregnancy is a non-viable pregnancy that develops outside of the womb. It occurs in two percent of all pregnancies. An ectopic pregnancy is usually located in one of the fallopian tubes. As the fetus grows, the tube cannot hold it, causing the tube to rupture (burst) and bleed. Unless they are discovered and treated early, almost 40 percent of ectopic pregnancies rupture suddenly, causing pain and bleeding in the abdominal cavity. The other 60 percent usually cause slow bleeding in the abdomen. Ruptured ectopic pregnancies can be fatal. The approved labeling for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg, states that the use of mifepristone, in a regimen with misoprostol, for the medical termination of pregnancy through ten weeks gestation is contraindicated in patients with confirmed or suspected ectopic pregnancy.

9. **Does the FDA endorse this drug product**

   The FDA does not endorse any drug product. The agency evaluates all drug applications submitted by applicants to determine whether the data and information in an application support the approval of the application. The same standards are applied to the drug applications for Mifeprex and the approved generic Mifepristone Tablets, 200 mg, as are applied to all drug applications.

The Mifepristone REMS Program

10. **Why is there a REMS for this product?**

    The FDA's determination as to whether a REMS is necessary for a particular drug is a drug-specific evaluation. The agency considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional risk mitigation measures beyond the FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.

    The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone when used for medical termination of pregnancy through ten weeks gestation by, among other things, requiring that prescribers have the necessary qualifications to assess whether patients are appropriate candidates for the drug and to provide necessary intervention in case of complications (or have made plans to provide such care through others), ensuring that mifepristone is only dispensed by certified pharmacies or by or under the supervision of certified prescribers, and requiring that patients be informed of the risks of the treatment regimen.

11. **What are the restrictions on prescribing and dispensing mifepristone for medical termination of pregnancy through ten weeks gestation?**

    When the agency reviewed and approved the original new drug application for Mifeprex (mifepristone) in 2000, it concluded that certain restrictions were necessary to ensure the safe use of the drug. These restrictions were approved as a risk evaluation and mitigation strategy (REMS) in 2011 and have been modified since then.

    These REMS requirements also apply to the approved generic version of Mifeprex. Mifeprex and the approved generic version of Mifeprex are subject to a single, shared system REMS, known as the Mifepristone REMS Program. This program sets the requirements that must be followed to ensure safe use of both Mifeprex and the approved generic version of Mifeprex.

    Under the Mifepristone REMS Program:

    - Mifepristone must be prescribed by a health care provider that meets certain qualifications and is certified under the Mifepristone REMS Program.
    - In order to become certified to prescribe mifepristone, health care providers must complete a Prescriber Agreement Form.
    - The Patient Agreement Form must be reviewed with and signed by the patient and the health care provider, and the risks of the mifepristone treatment regimen must be fully explained to the patient before prescribing mifepristone.
    - The patient must be provided with a copy of the Patient Agreement Form and mifepristone Medication Guide (FDA-approved information for patients).
    - Mifepristone may only be dispensed by or under the supervision of a certified prescriber, or by a certified pharmacy on a prescription issued by a certified prescriber.

- To become certified to dispense mifepristone, pharmacies must complete a Pharmacy Agreement Form.
- Certified pharmacies must be able to ship mifepristone using a shipping service that provides tracking information.
- Certified pharmacies must ensure mifepristone is dispensed to the patient in a timely manner.

Each REMS is required to have a plan for periodic assessments by the applicant, which are reviewed by the agency to determine whether the REMS is meeting its goals or whether certain goals or elements of the REMS must be modified. FDA may require applicants to modify a REMS if the agency determines that an element is no longer necessary to ensure that the benefits of the drug outweigh the risks or to minimize the burden on the health care delivery system.

12. **How does the Mifepristone REMS Program ensure safe use of the drug?**

    The Mifepristone REMS Program requires that in order for patients to receive mifepristone, it must be prescribed by a certified prescriber who meets certain qualifications. Under the Mifepristone REMS Program, mifepristone must be dispensed by or under the supervision of a certified prescriber or by certified pharmacies on prescriptions issued by certified prescribers. The Mifepristone REMS Program is a closed system, meaning prescribers, pharmacies, and distributors are certified or authorized and verified under the REMS prior to distribution or dispensing of the drug. The Mifepristone REMS Program ensures that mifepristone is only distributed to health care providers and pharmacies that have agreed to the REMS requirements.

13. **How does the Mifepristone REMS Program approved in January 2023 differ from the previous REMS requirements?**

    Prior to the modifications to the Mifepristone REMS Program in January 2023, the Mifepristone REMS Program required certified prescribers to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. The requirement to dispense directly to the patient in one of these settings was referred to as the "in-person dispensing requirement." There were periods when the in-person dispensing requirement was not being enforced. First, from July 13, 2020, until January 12, 2021, the FDA was enjoined from enforcing the in-person dispensing requirement by an injunction issued in the *ACOG v. FDA* litigation. On April 12, 2021, the agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 public health emergency.

    In 2021, after conducting a comprehensive review of the Mifepristone REMS Program, the FDA determined, based on the available data and information, that the REMS must be modified to reduce burden on the health care delivery system and to ensure the benefits of the product outweigh the risks. On December 16, 2021, the FDA announced that the modifications to the Mifepristone REMS Program would consist of:

    - Removing the "in-person dispensing requirement"

- Adding a requirement that pharmacies that dispense the drug be certified

Consistent with the typical process for REMS modifications, the FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg. Following receipt of these letters, the applicants prepared a proposed REMS modification and submitted it to their respective applications. Those submissions were reviewed and approved on January 3, 2023. The REMS document and materials are available on the FDA website at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm).

14. **Where can patients get mifepristone for medical termination of pregnancy through ten weeks gestation?**

    Mifepristone must be prescribed by a certified prescriber who meets certain qualifications and agrees to follow certain guidelines for use. Under the Mifepristone REMS Program, mifepristone can be dispensed by or under the supervision of a certified prescriber or by a certified pharmacy on a prescription issued by a certified prescriber.

15. **What qualifications must health care providers have to become certified to prescribe mifepristone for medical termination of pregnancy through ten weeks gestation?**

    Health care providers who would like to become certified to prescribe mifepristone must review the Prescribing Information for mifepristone and must have the ability to date pregnancies accurately and the ability to diagnose ectopic pregnancies. Health care providers must also be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care. Health care providers must be able to ensure that patients have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form.

    Some states allow health care providers other than physicians to prescribe medications. Health care providers should check their individual state laws.

16. **Are patients required to see a health care provider in person before obtaining mifepristone for medical termination of pregnancy through ten weeks gestation?**

    No. The Mifepristone REMS Program does not require patients to see a health care provider in person before obtaining mifepristone for medical termination of pregnancy through ten weeks gestation. Mifeprex and the approved generic Mifepristone Tablets, 200 mg, are indicated, in a regimen with misoprostol, to terminate a pregnancy up to 70 days gestation and contraindicated for certain patients, including those with an ectopic pregnancy. The FDA has determined that it is not necessary for the REMS to mandate how providers clinically assess patients for duration of pregnancy and for ectopic pregnancy. The prescription labeling for Mifeprex and the approved generic provide guidance to prescribers regarding how they can confirm the gestational age of the pregnancy and confirm that the pregnancy is located in the

uterus. Aspects of a patient's medical history that may constitute contraindications to medical termination of pregnancy may be elicited without direct physical contact with the certified prescriber and can be done in different types of health care settings, thus certified prescribers are not necessarily required to be physically present with the patient when they prescribe mifepristone. As explained above (Question 15), health care providers certified under the Mifepristone REMS Program must also be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care and must be able to ensure that patients have access to medical facilities for emergency care.

17. **What information did the FDA consider when it reviewed the Mifepristone REMS Program in 2021?**

    To determine whether a modification to the Mifepristone REMS Program was warranted, the FDA conducted a comprehensive review of the published literature, other relevant safety and adverse event data, and information provided by advocacy groups, individuals and the applicants related to the modifications that were under consideration. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation.

18. **Prior to the FDA's action in January 2023, how was mifepristone dispensed to patients?**

    Prior to the FDA's action on the REMS modification applications submitted by the applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, the Mifepristone REMS Program required certified prescribers to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. The requirement to dispense directly to the patient in one of these settings was referred to as the "in-person dispensing requirement."

    There were periods when the in-person dispensing requirement was not being enforced. First, from July 13, 2020, until January 12, 2021, the FDA was enjoined from enforcing the in-person dispensing requirement by an injunction issued in a lawsuit, *ACOG v. FDA* filed in the U.S. District Court for the District of Maryland. On April 12, 2021, the agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 public health emergency.

    During the periods when the in-person dispensing requirement was not being enforced, the applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, used mail order pharmacies to receive and hold mifepristone on behalf of the certified prescribers who purchased the product. Pursuant to a prescription for Mifeprex or its approved generic, the mail order pharmacy would ship the product to a named patient.

19. **What is the FDA's role in overseeing the Mifepristone REMS Program?**

    As with all REMS, the FDA monitors the applicants' compliance with the Mifepristone REMS Program, including by reviewing periodic assessment information from the applicants and conducting on-site inspections, and takes action as appropriate.

20. **What is pharmacy certification and why is it a requirement of the Mifepristone REMS Program?**

    The Mifepristone REMS Program requires all pharmacies that dispense mifepristone to be specially certified. The pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Any pharmacy that meets the requirements of the Mifepristone REMS Program is eligible to be certified. To learn more about pharmacy certification requirements, review the Mifepristone REMS Program documents (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390#tabs-4).

21. **What steps are required for pharmacy certification?**

    The pharmacy certification requirement ensures that pharmacies are aware of and agree to follow applicable REMS requirements and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers.

    To become certified to dispense mifepristone, pharmacies must: (1) be able to receive Prescriber Agreement Forms by email and fax; (2) be able to ship mifepristone using a shipping service that provides tracking information; (3) designate an authorized representative to carry out the certification process on behalf of the pharmacy; and (4) ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program, which includes, among other requirements, the completion of a Pharmacy Agreement Form.

22. **Is mifepristone available at retail pharmacies?**

    The January 2023 modification to the Mifepristone REMS Program removed the restriction that did not allow mifepristone to be dispensed from retail pharmacies. While pharmacy certification is required, any pharmacy that meets the requirements of the Mifepristone REMS Program is eligible for certification.

23. **Is mifepristone available for over-the-counter use?**

    No. Mifepristone for medical termination of a pregnancy through ten weeks gestation is currently only available by prescription. An applicant seeking to switch mifepristone for medical termination of pregnancy through ten weeks gestation from prescription to nonprescription (also referred to as over-the-counter) status would need to submit this information to the FDA for evaluation. In order for a drug product to be approved for nonprescription use (including switching a prescription drug product to nonprescription marketing), the applicant must provide sufficient information demonstrating that the drug can be used safely and effectively by consumers without the supervision of a health care provider.

24. **What would be required to remove the REMS?**

The FDA may release a REMS or remove certain components of a REMS, if, after review of REMS assessments or other information, the agency determines that the extra measures in a REMS are no longer necessary to ensure a medication's benefits outweigh its risks.

Additional Information

25. **Is it possible for an individual to become pregnant again after taking mifepristone for medical termination of pregnancy through ten weeks gestation?**

    It is possible for an individual to become pregnant again soon after a pregnancy ends. A patient should consult with their health care provider regarding any specific questions they may have.

26. **Is mifepristone approved in any other countries for medical termination of pregnancy?**

    Mifepristone for medical termination of pregnancy has been approved in France since 1988, and also is approved in the United Kingdom, Sweden, and approximately 80 other countries.

27. **Does the FDA set the price of mifepristone and is the drug reimbursed by health insurance providers?**

    The FDA does not have the authority to regulate the prices of drug products in the United States. Manufacturers, distributors, and retailers establish the prices. Additionally, the FDA does not have input into or legal control over whether an insurance company does or does not cover the cost of a drug. Insurance coverage is a decision made by an insurance provider. Individuals should contact their insurance provider if they have questions about whether a particular insurance provider will cover the cost of the drug.

28. **Has FDA ever taken action regarding the sale of mifepristone online?**

    The FDA has sent warning letters to websites selling unapproved and misbranded mifepristone and misoprostol over the internet, including AidAccess (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019) and Rablon (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/rablon-1111111-03082019).

    There have also been several criminal cases related to the online sale of mifepristone for medical termination of pregnancy. We are aware of three cases about which the Agency can speak publicly. The first is *United States v. O'Neil*, in the U.S. District Court for the District of Maryland. Information about two more individual prosecutions are available here: March 28, 2017: Former Atlantic County, New Jersey, Man Charged with Smuggling and Dispensing Misbranded Drugs | FDA (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/march-28-2017-former-atlantic-county-new-jersey-man-charged-smuggling-and-dispensing-misbranded) and here: New York Woman Sentenced for Selling Abortion-Inducing Pills Illegally Smuggled Into US | USAO-WDWI | Department of Justice (https://www.justice.gov/usao-wdwi/pr/new-york-woman-sentenced-selling-abortion-inducing-pills-illegally-smuggled-us). The FDA also issued a Final Debarment Order for Ursula

Wing (https://www.federalregister.gov/documents/2021/03/26/2021-06258/ursula-wing-final-debarment-order), debarring her for a period of five years from importing or offering for import any drug into the United States. This debarment was based on her felony conviction (https://www.justice.gov/usao-wdwi/pr/new-york-woman-sentenced-selling-abortion-inducing-pills-illegally-smuggled-us) related to her importation and distribution of unapproved and misbranded mifepristone and misoprostol over the internet.

Litigation and Other Legal Issues

29. **Was the Mifepristone REMS Program modified in 2023 in response to the Supreme Court's 2022 decision in *Dobbs v. Jackson Women's Health Organization*?**

    No. The agency's comprehensive review of the Mifepristone REMS Program, which led to the 2021 decision that a modification was required, is related to the litigation in *Chelius v. Becerra*. In accordance with the typical process for REMS modifications, the FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg. Following receipt of these letters, the applicants prepared a proposed REMS modification and submitted it to their respective applications. The FDA reviewed the REMS modification supplements submitted by the applicants in the Mifepristone REMS Program and approved a REMS modification that removes the in-person dispensing requirement and adds pharmacy certification.

30. **Was the Mifepristone REMS Program modified in 2023 in response to state abortion laws?**

    No. See response to Question 29.

31. **What happens if a state refuses to allow mifepristone to be prescribed for medical termination of pregnancy?**

    We are coordinating with the Department of Justice and others across the government on these legal issues. Any questions regarding preemption of state law should be directed to the Department of Justice.

32. **What is the status of the *Alliance for Hippocratic Medicine* lawsuit about the approval of mifepristone?**

    On November 18, 2022, the FDA and HHS were sued in the U.S. District Court for the Northern District of Texas by the Alliance for Hippocratic Medicine and other plaintiffs. The agency generally does not comment on pending litigation.

The January 2023 REMS Modification

33. **What action did the FDA take on the Mifepristone REMS Program in January 2023?**

In response to the REMS Modification Notification letters sent on December 16, 2021, to the applicants for Mifeprex and the approved generic Mifepristone Tablets, 200 mg, the applicants submitted supplemental applications to modify the Mifepristone REMS Program to remove the in-person dispensing requirement and add pharmacy certification. The FDA reviewed the applicants' supplemental applications, as amended, and approved a modification to the Mifepristone REMS Program. Under the Mifepristone REMS Program, as modified, Mifeprex and its approved generic can be dispensed by or under the supervision of a certified prescriber or by certified pharmacies on a prescription issued by a certified prescriber.

The Mifepristone REMS Program continues to require the Patient Agreement Form and certification of health care providers who prescribe mifepristone.

The revised REMS document and materials are available on the FDA website at Approved Risk Evaluation and Mitigation Strategies (REMS) (http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm).

34. **What was the process for approving the current REMS modification?**

In 2021, in order to determine whether a modification to the Mifepristone REMS Program was warranted, the FDA conducted a comprehensive review of the published literature, other relevant safety and adverse event data, and information provided by advocacy groups, individuals, and the applicants related to the modifications that were under consideration. After conducting this review, the FDA determined that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification. In accordance with the typical process for REMS modifications, the FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg. Following receipt of these letters, the applicants prepared a proposed REMS modification and submitted it to their respective applications. The approved REMS document and materials are available here (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390#tabs-4).

35. **Why did the FDA conduct a review of the Mifepristone REMS Program in 2021?**

REMS require applicants to prepare and submit periodic assessments, which are reviewed by the agency to determine whether the REMS is meeting its goals or whether certain goals or elements of the REMS must be modified.

The agency's comprehensive review of the Mifepristone REMS Program, which led to the agency's December 16, 2021, decision that a modification was required, was related to the litigation in *Chelius v. Becerra*, as well as to the regular periodic assessments of the REMS. On May 7, 2021, the FDA and the plaintiffs in *Chelius* filed a joint motion to stay that litigation, which involves the single, shared system REMS for Mifeprex and its approved generic, Mifepristone Tablets, 200 mg. The court granted the stay on May 7, 2021. The *Chelius* case was reopened on February 28, 2023, and the plaintiffs now challenge the modified Mifepristone REMS Program. The agency generally does not comment on pending litigation.

36. **Was there a change in the reported adverse events during the pandemic when the in-person dispensing requirement was not enforced?**

No. There were periods when the in-person dispensing requirement was not being enforced. First, from July 13, 2020, until January 12, 2021, the FDA was enjoined from enforcing the in-person dispensing requirement by an injunction issued in the *ACOG v. FDA* litigation. On April 12, 2021, the agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 public health emergency. The FDA analyzed postmarketing data to determine if there was a difference in adverse events between periods when in-person dispensing was and was not enforced. Based on this review, the agency concluded that there did not appear to be a difference in adverse events between periods when in-person dispensing was and was not enforced.

Exhibit 4

Medication Abortion Now Accounts for More Than Half of All US Abortions

Year
January 1, 2022
Rachel K. Jones, Guttmacher Institute, Elizabeth Nash, Guttmacher Institute, Lauren Cross, Guttmacher Institute, Jesse Philbin, Guttmacher Institute and Marielle Kirstein, Guttmacher Institute

Updated on December 1, 2022:

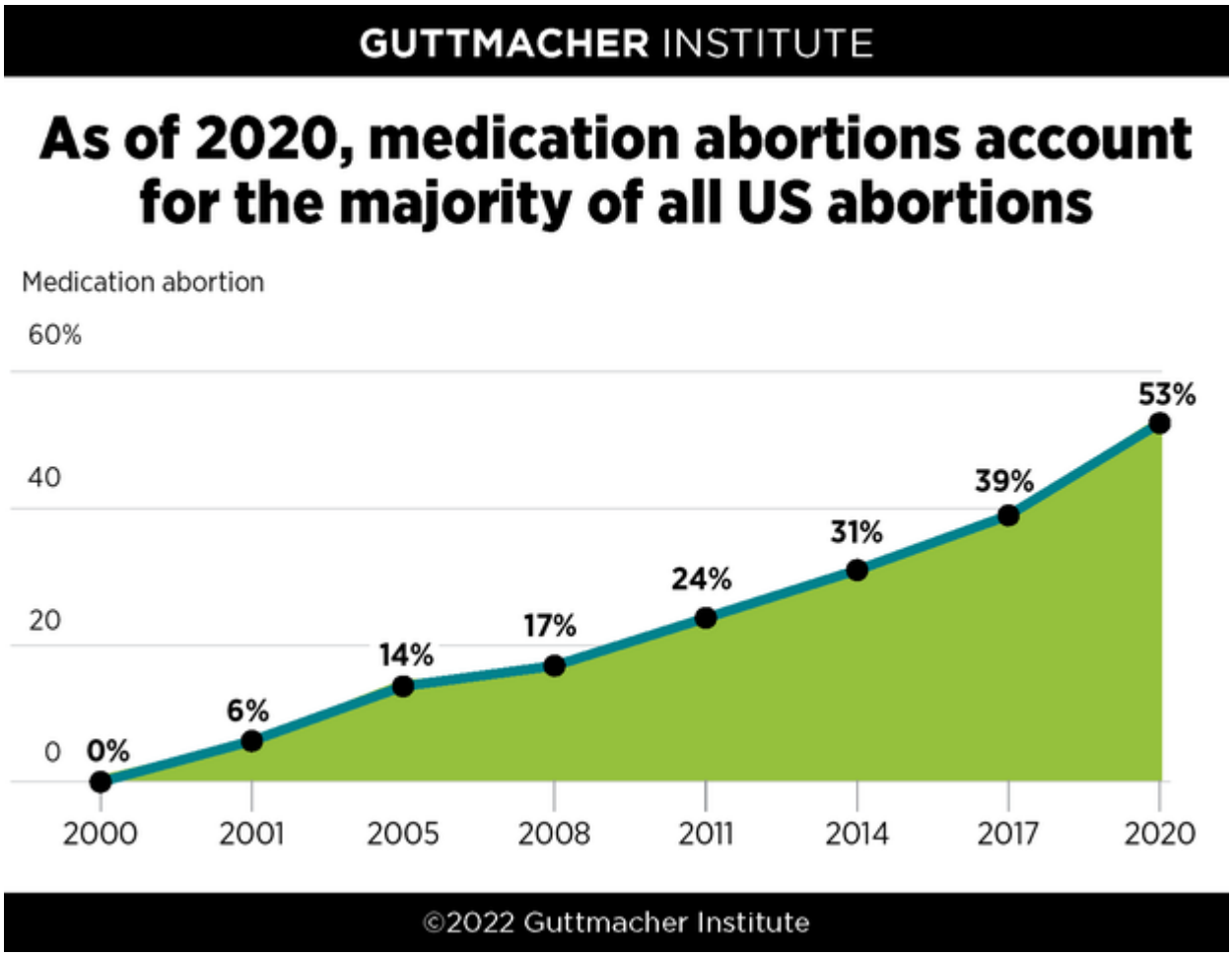
This analysis and accompanying graphic have been updated to reflect the final data from Guttmacher's census of all known abortion providers, which found that medication abortion accounted for 53% of all facility-based abortions in the United States in 2020. Preliminary data, originally published on February 24, 2022, indicated that medication abortion accounted for 54% of all abortions.

The full 2020 Abortion Provider Census can be found here.

First published on February 24, 2022:

In 2000, the US Food and Drug Administration (FDA) approved mifepristone as a method of abortion. Taken along with misoprostol, the two-drug combination is known as medication abortion or the "abortion pill." New research from the Guttmacher Institute shows that 20 years after its introduction, medication abortion accounted for more than half of all abortions in the United States.

Guttmacher Institute's periodic census of all known abortion providers show that in 2020, medication abortion accounted for 53% of US abortions. That year is the first time medication abortion crossed the threshold to become the majority of all abortions and it is a significant jump from 39% in 2017, when Guttmacher last reported these data. Preliminary data originally published in February 2022 showed that medication abortion accounted for 54% of all abortions in the US.



This new data point powerfully illustrates that medication abortion has gained broad acceptance from both abortion patients and providers. It also underscores how central this method has become to US abortion provision, thanks to its track record of safe and effective use for more than two decades. As medication abortion has become the most common method of abortion, there is still the potential to further increase access—which is why the method has become a main target of anti-abortion politicians and activists seeking to restrict care.

Medication Abortion Is a Safe and Effective Option

Currently, medication abortion is approved for use up to 10 weeks of pregnancy. The FDA approved that limit based on research the agency reviewed at the time. However, additional research shows provision beyond 10 weeks is safe and effective and some providers administer medication abortion "off label" after that point in pregnancy.

Patients initiate a medication abortion by taking mifepristone, followed by misoprostol one or two days later, as directed by a provider or the manufacturer's instructions. Medication abortion differs from procedural abortion, which is provided in a clinical setting via vacuum aspiration or another method. Patients should always have the full scope of options available to them, including in-person care with a clinician.

Medication abortion can be completed outside of a medical setting—for example, in the comfort and privacy of one's home. Pills can be provided at a clinic or delivered directly to a patient through the mail. The latter option can be especially useful in addressing logistical burdens abortion patients often face when they have to visit a provider to obtain care, such as arranging for child care and

time off work and paying for transportation costs. And, in areas of the country that are rural or underserved by providers, medication abortion can save a patient hundreds of miles of travel.

Throughout the more than 20 years that it has been used in the United States, medication abortion has been proven to be overwhelmingly safe and effective.

- A comprehensive review of the science related to the provision of abortion care in the United States conducted by the National Academies of Sciences, Engineering, and Medicine confirmed that medication abortion has a very low rate of serious complications and is effective at ending an early pregnancy.

- Subsequent research has demonstrated that direct-to-patient medication abortion provided via telemedicine—where the patient remotely consults with a provider and pills are shipped through the mail—is likewise safe and effective and works well for patients.

Transforming the Landscape of Abortion in the United States

A number of factors have transformed the landscape around medication abortion in recent years. While the use of medication abortion has been steadily increasing since it was first approved, the COVID-19 pandemic likely accelerated that trend. Since the start of the pandemic in early 2020, there has been increased attention on the benefits of telehealth—and abortion has very much been a part of that conversation.

Another factor improving access has been an increase in evidence-based policies that allow non-physician medical professionals—such as physician assistants and advanced practice nurses—to provide medication abortion. Broadening the pool of qualified providers is in line with expert guidance. There has also been an increase in clinics that only provide medication abortion and not procedural care.

Despite its long-standing safety record, mifepristone has been subject to a medically unwarranted Risk Evaluation and Mitigation Strategy (REMS) imposed by the FDA with the drug's approval in 2000. Under the requirements of this restriction, the medication had to be dispensed only by certified prescribers, patients had to sign an agreement stating they were told about potential side effects of the medication and pills had to be dispensed in clinics, medical offices or hospitals (not pharmacies).

In April 2021, the FDA announced it would allow abortion pills to be mailed to patients for the duration of the pandemic. This action meant patients could obtain an abortion without making one (or several) in-person visits to a health care facility and risking unnecessary exposure to COVID-19. The change also allowed online-only abortion providers to mail pills to patients in more states.

After years of petitions to reevaluate the REMS based on mifepristone's decades-long safety record, the FDA issued a permanent decision in December 2021 to allow mailing of the pills and also expanded access through pharmacies. However, guidelines on pharmacy access have not yet been developed.

State Policies Determine Level of Access

Because medication abortion is a great option for patients and can be taken safely and effectively outside of a clinic setting, it has long been a target of abortion opponents. The lifting of mailing restrictions has predictably encouraged abortion opponents to quickly enact additional burdensome and medically unnecessary restrictions on medication abortion. These attacks have been paired with renewed efforts to misrepresent the method's safety record and otherwise attempt to stigmatize it and deter its use.

As part of that larger strategy, anti-abortion policymakers have long pursued state-level restrictions to limit access to medication abortion, a push that may further intensify this year. As of February 2022:

- In 32 states, clinicians who administer medication abortion are required to be physicians, even though medical professionals with different titles and specialties are otherwise allowed to prescribe medications, oversee treatments and manage patients' health.
    - This is an effort to limit the availability of medication abortion, which particularly affects patients in rural or underserved areas where there may not be consistent access to a physician.
- Texas prohibits the use of medication abortion starting at seven weeks of pregnancy, which is a politically determined limit at odds with current medical guidance. Indiana bans its use at 10 weeks, which corresponds to current FDA guidance, but prevents expanded access in the future.
- In 19 states, the clinician providing a medication abortion must be physically present when the medication is administered, thereby prohibiting the use of telemedicine to prescribe medication for abortion.
- In three states, mailing abortion pills to patients is currently banned (Arizona, Arkansas and Texas); mailing bans in another three states (Montana, Oklahoma and South Dakota) have been blocked by courts.
- In January 2022, South Dakota approved regulations that would have required patients to make four trips to a clinic in order to obtain a medication abortion. Enforcement of these regulations has been blocked pending the outcome of litigation.
- Already this year (as of February 22, 2022), 16 state legislatures have introduced bans or restrictions on medication abortion, including legislation that would ban the use of medication abortion in seven states (Alabama, Arizona, Illinois, Iowa, South Dakota, Washington and Wyoming), specifically prohibit the mailing of abortion pills in five states (Georgia, Kentucky, Maryland, Massachusetts and Nebraska) and bar the use of telehealth to provide medication abortion in eight states (Georgia, Iowa, Kentucky, Massachusetts, Minnesota, Nebraska, South Dakota and Tennessee).

Challenges and Opportunities Ahead

Given the reality of the 6-3 anti-abortion majority on the US Supreme Court that is now primed to severely weaken or overturn *Roe v. Wade* outright, medication abortion is likely to become even more critical in the delivery of care to many people who may be unable to access care in a clinic, as well as the target of additional ideological attacks.

A recent Guttmacher analysis predicts that if *Roe v. Wade* is overturned, there are 26 states certain or likely to quickly ban abortion to the fullest extent allowed by the Supreme Court. For medication abortion, additional restrictions could include more states passing a ban on mailing of medications or even attempts to block legal channels for patients to receive this care by leaving their home state.

Before abortion was legalized across the country in 1973, quality of care and health risks were widespread concerns for patients without legal access to the procedure. Given general medical advancements in the past 50 years and mifepristone's safety record during more than 20 years of use, a larger worry among medical professionals and advocates today is the potential legal risk to patients, providers and anyone who assists someone in obtaining a medication abortion in states

where it may be banned or criminalized. Actions that pose a risk for prosecution could include obtaining pills through alternative channels, such as online providers and clinics across state lines.

Such a scenario is likely to further exacerbate existing racist and discriminatory law enforcement practices that target and disproportionately criminalize Black, brown and other people of color for their pregnancy outcomes. Furthermore, people of color account for the majority of abortion patients in the United States and they will be the most severely affected by denial of abortion care.

Looking at this landscape, states with policies supportive of abortion rights must redouble their efforts to further codify, reinforce and expand those protective policies. Federal action is also needed to put a stop to the barrage of state-level restrictions and attempts at outright bans on the use of medication abortion. The Women's Health Protection Act is federal legislation that would protect access to abortion—whether someone lives in California or Texas—by establishing a right under federal law to deliver and receive abortion care without medically unnecessary restrictions and bans, including restrictions on the use of telehealth for medication abortion.

The introduction and availability of medication abortion has proven to be a game changer in expanding abortion care in the United States, and it will likely be an even more important option for people to obtain an abortion as many states continue to pass legislation to bar or restrict abortion access.

Methodology

Every three years, the Guttmacher Institute contacts all known facilities providing abortion in the country to collect information about service provision, including the total number of medication abortions provided. The most recent survey, collecting information for 2019 and 2020, is available here. Preliminary data, published in February 2022, reflected information obtained from approximately 75% of US clinics that provided abortion care in 2020; the final proportion of all abortions represented by medication abortion changed by only one percentage point. These counts only include provision of medication abortion overseen by clinicians and do not account for self-managed abortion.

Hospitals accounted for only 3% of abortions provided in all survey years. Figures in the above graphic for 2000–2014 do not include abortions provided in hospitals, while those for 2017 and 2020 do. If figures were adjusted to account for that share, the proportion of all abortions that were medication abortions in 2000–2014 would be the same or one percentage point lower.

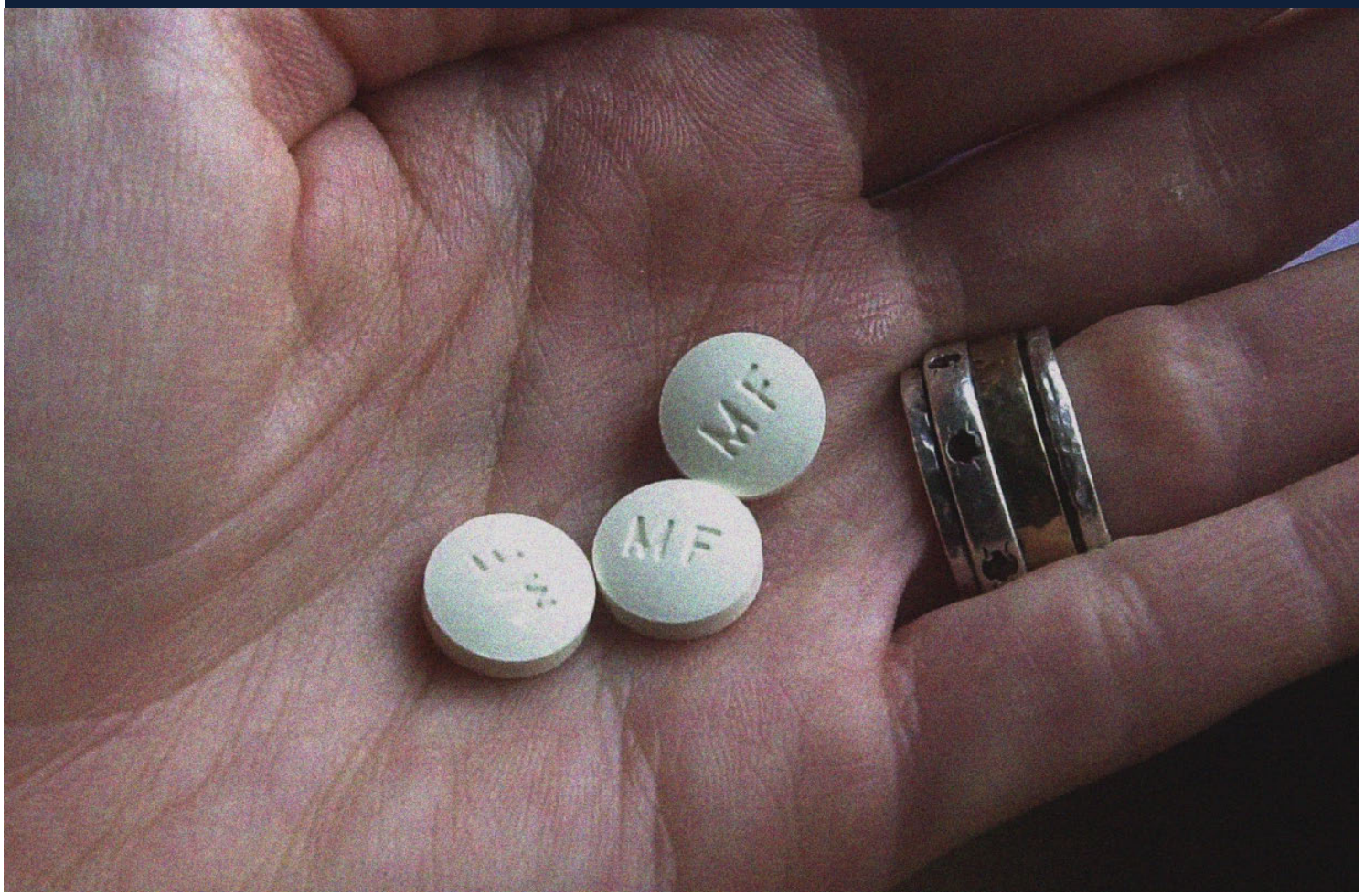
Source URL: *https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions*

Exhibit 5

DATA GRAPHICS

Map: Where medication abortion is and isn't legal

A consequential lawsuit in Texas seeks to upend the FDA's approval of the abortion pill mifepristone.



Mifepristone is one of the two drugs used in medication abortions.

Bill Greenblatt / Getty Images file

Feb. 21, 2023, 4:06 PM CST / Updated Aug. 16, 2023, 2:43 PM CDT

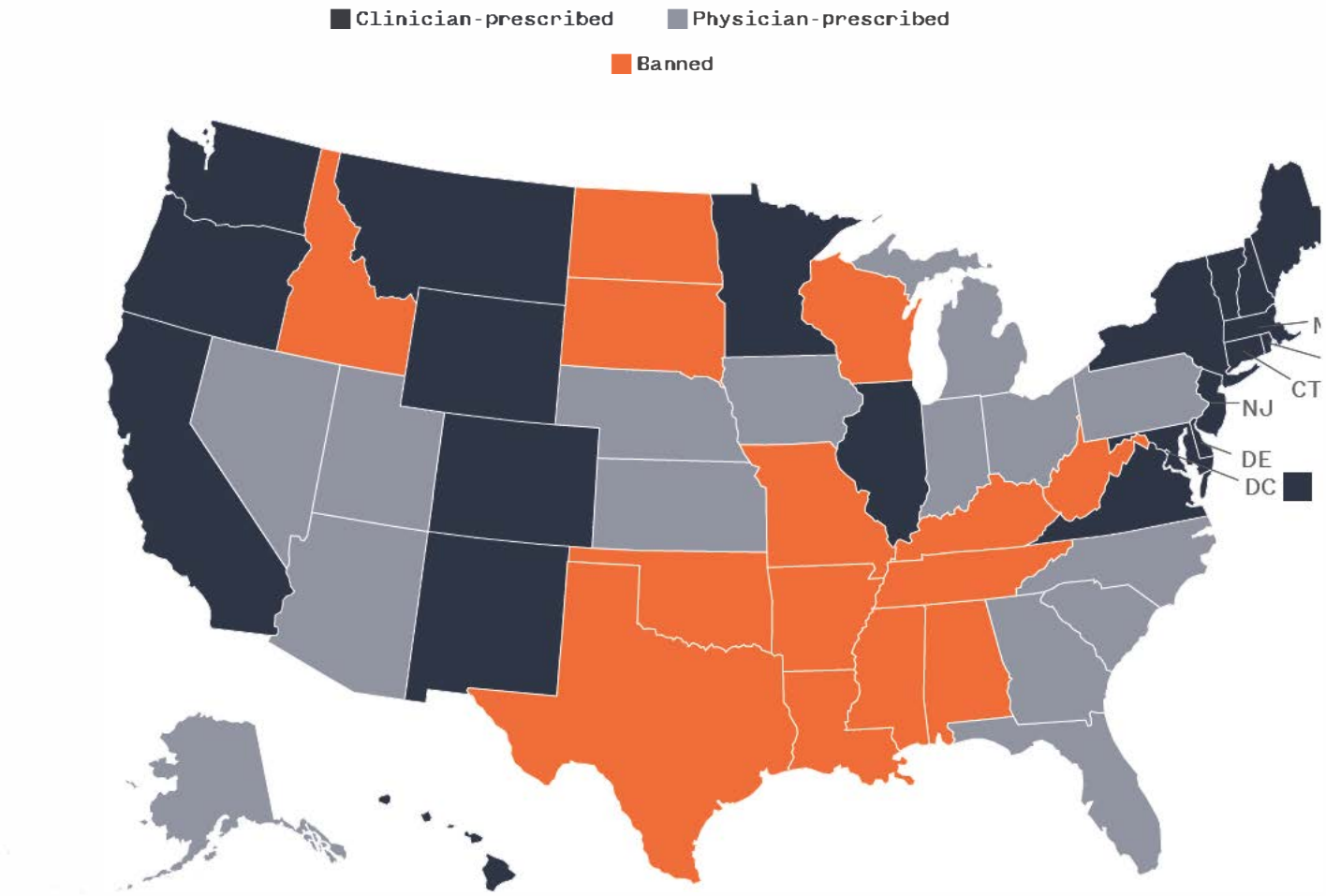
By Jasmine Cui and Danica Jefferies

In a consequential lawsuit filed in Texas, an anti-abortion group is seeking to upend the Food and Drug Administration's approval of abortion pills by raising issues with the process used to evaluate and eventually greenlight the drugs decades ago.

Access to the two-drug regimen is currently legal in some form in 36 states and Washington, D.C.: Medication abortion is legal in 21 states and restricted in the remaining 15, according to data from the Guttmacher Institute, a research organization that advocates for abortion access.

Where medication abortion is legal

Medication abortion is legal in 21 states and Washington, D.C., but in 15 states must be prescribed by a doctor, not other clinicians.



State	Legality	Notes
Alabama	Banned	
Alaska	Physician-prescribed	
Arizona	Physician-prescribed	Patient must have in-person physician visit, and mailing of abortion pills is banned.

Arkansas	Banned	
California	Clinician-prescribed	
Colorado	Clinician-prescribed	
Connecticut	Clinician-prescribed	
Delaware	Clinician-prescribed	
District of Columbia	Clinician-prescribed	
Florida	Physician-prescribed	
Georgia	Physician-prescribed	Georgia has a 6-week gestational age limit for abortions.
Hawaii	Clinician-prescribed	
Idaho	Banned	
Illinois	Clinician-prescribed	
Indiana	Physician-prescribed	Patient must have in-person physician visit.
Iowa	Physician-prescribed	
Kansas	Physician-prescribed	
Kentucky	Banned	
Louisiana	Banned	
Maine	Clinician-prescribed	
Maryland	Clinician-prescribed	
Massachusetts	Clinician-prescribed	
Michigan	Physician-prescribed	
Minnesota	Clinician-prescribed	
Mississippi	Banned	
Missouri	Banned	
Montana	Clinician-prescribed	

Nebraska	Physician-prescribed	Patient must have in-person physician visit.
Nevada	Physician-prescribed	
New Hampshire	Clinician-prescribed	
New Jersey	Clinician-prescribed	
New Mexico	Clinician-prescribed	
New York	Clinician-prescribed	
North Carolina	Physician-prescribed	Patient must have in-person physician visit.
North Dakota	Banned	
Ohio	Physician-prescribed	
Oklahoma	Banned	
Oregon	Clinician-prescribed	
Pennsylvania	Physician-prescribed	
Rhode Island	Clinician-prescribed	
South Carolina	Physician-prescribed	Patient must have in-person physician visit.
South Dakota	Banned	
Tennessee	Banned	
Texas	Banned	
Utah	Physician-prescribed	
Vermont	Clinician-prescribed	
Virginia	Clinician-prescribed	
Washington	Clinician-prescribed	
West Virginia	Banned	
Wisconsin	Banned	
Wyoming	Clinician-prescribed	

Show less

Notes: Data current as of July 1, 2023.

Source: Guttmacher Institute

U.S. District Judge Matthew Kacsmaryk's decision in the Texas case has the potential to influence access to abortion pills for the 58.8 million U.S. women of reproductive age who do not live in a state where abortion is banned.

The group suing the FDA has asked for a preliminary injunction to take one of the two drugs used in a medication abortion, mifepristone, off the market while the case plays out. If Kacsmaryk grants the injunction request and the FDA follows the court's order, access to medication abortion as we know it could be blocked nationwide.

Meanwhile, the FDA finalized a rule in January that allows pharmacies to fill prescriptions for the pills required for medication abortions.

Medication abortion accounted for more than half of all U.S. abortions in 2020, according to the Guttmacher Institute.

———Jasmine Cui

Jasmine Cui is a reporter for NBC News.

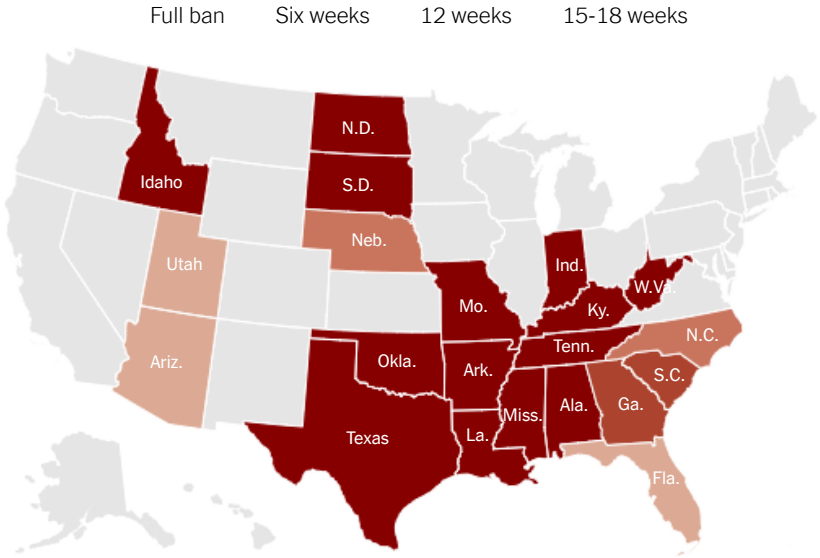
———Danica Jefferies

Danica Jefferies is an intern with the Data Graphics team for NBC News

Exhibit 6

Tracking Abortion Bans Across the Country

By The New York Times Updated Jan. 8, 09:30 A.M. ET



Twenty-one states ban abortion or restrict the procedure earlier in pregnancy than the standard set by Roe v. Wade, which governed reproductive rights for nearly half a century until the Supreme Court overturned the decision last year.

In some states, the fight over abortion access is still taking place in courtrooms, where advocates have sued to block bans and restrictions. Other states have moved to expand access to abortion by adding legal protections.

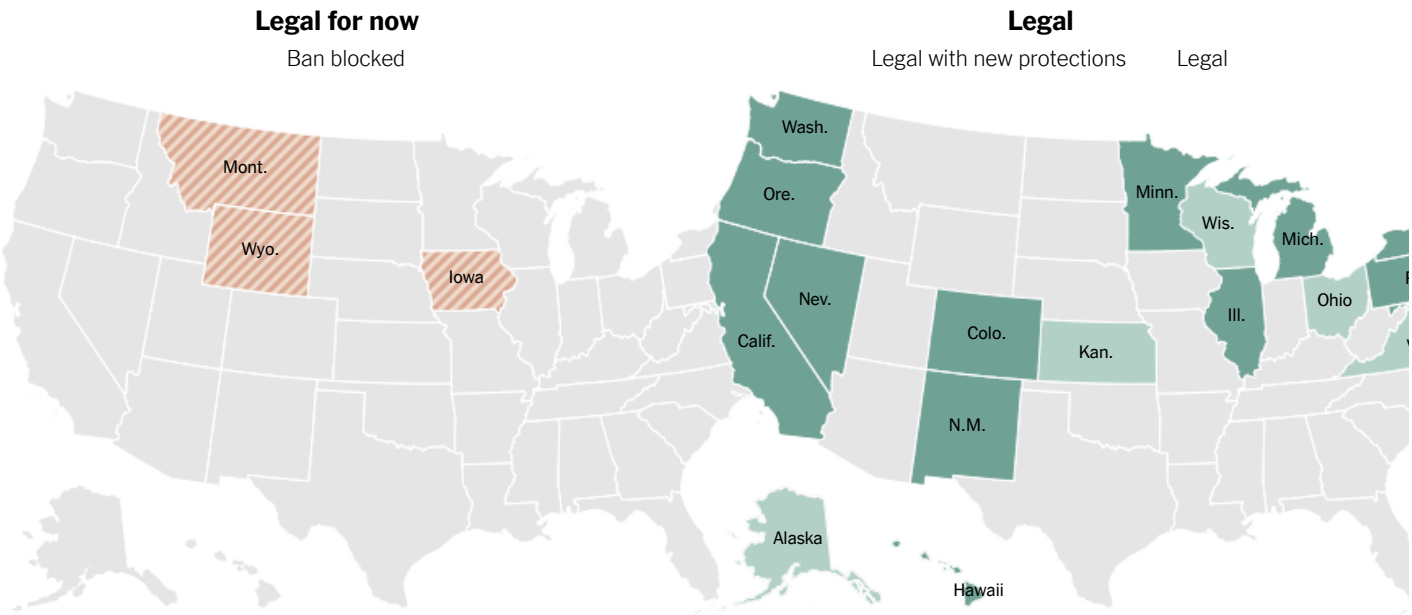
Latest updates

- The U.S. Supreme Court agreed to hear a challenge to Idaho's near-total ban on abortions in April.

The New York Times is tracking abortion laws in each state after the Supreme Court's decision in Dobbs v. Jackson Women's Health Organization, which ended the constitutional right to an abortion.

Where abortion is legal

In a few states that have enacted bans or restrictions, abortion remains legal for now as courts determine whether these laws can take effect. Abortion is legal in the rest of the country, and many states have added new protections since Dobbs.



State details

More details on the current status of abortion in each state are below.

Search states

STATE	STATUS OF ABORTION	LEGAL UNTIL
Alabama	Banned	—
Abortion is banned in almost all circumstances.		
Arkansas	Banned	—
Abortion is banned in almost all circumstances.		

STATE	STATUS OF ABORTION	LEGAL UNTIL
Idaho	Banned	—
Abortion is banned in almost all circumstances. In January, the Idaho Supreme Court ruled there is no constitutional right to an abortion.		
Indiana	Banned	—
Abortion is banned in almost all circumstances. In August, the Indiana Supreme Court certified a June ruling that the state's abortion ban did not violate the state Constitution. A separate challenge to the ban, by residents who argue it violates their religious rights, is ongoing.		
Kentucky	Banned	—
Abortion is banned in almost all circumstances. Last fall voters rejected a ballot measure that would have amended the state Constitution to say it contains no right to an abortion.		
Louisiana	Banned	—
Abortion is banned in almost all circumstances.		
Mississippi	Banned	—
Abortion is banned in almost all circumstances.		
Missouri	Banned	—
Abortion is banned in almost all circumstances.		
North Dakota	Banned	—
Abortion is banned in almost all circumstances.		
Oklahoma	Banned	—
Abortion is banned in almost all circumstances.		
South Dakota	Banned	—
Abortion is banned in almost all circumstances.		

STATE	STATUS OF ABORTION	LEGAL UNTIL
Tennessee	Banned	—
Abortion is banned in almost all circumstances.		
Texas	Banned	—
Abortion is banned in almost all circumstances. Private citizens can sue abortion providers and those who assist patients seeking an abortion after about six weeks of pregnancy.		
West Virginia	Banned	—
Abortion is banned in almost all circumstances.		
Georgia	Gestational limit	6 weeks
Abortion is banned after about six weeks of pregnancy. In October, the State Supreme Court reversed a lower court's ruling that the 2019 ban was void. The lower court must still weigh whether the ban violates the state's Constitution.		
South Carolina	Gestational limit	6 weeks
Abortion is banned after about six weeks of pregnancy. The South Carolina Supreme Court upheld the ban in August, after ruling in January that a similar ban from 2021 was unconstitutional.		
Nebraska	Gestational limit	12 weeks
Abortion is banned after 12 weeks of pregnancy. Gov. Jim Pillen signed the ban in May, after weeks of debate in the unicameral legislature and a failed attempt to pass a six-week ban.		
North Carolina	Gestational limit	12 weeks
Abortion is banned after 12 weeks of pregnancy. A federal judge temporarily blocked a provision that providers said could have limited their ability to offer the abortion pill to patients in the first weeks of pregnancy.		
Arizona	Gestational limit	15 weeks
Abortion is banned after 15 weeks of pregnancy. Enforcement of a separate ban on abortion from 1864 is blocked by an appeals court.		

STATE	STATUS OF ABORTION	LEGAL UNTIL
Florida	Gestational limit	15 weeks

Abortion is banned after 15 weeks of pregnancy. In April, Gov. Ron DeSantis signed a new ban on abortion after six weeks of pregnancy. That measure is not in effect pending a review by the Florida Supreme Court of the state's abortion laws. The court recognized the right to an abortion in Florida's Constitution three decades ago, but it has since become more conservative.

Utah	Gestational limit	18 weeks

Abortion is banned after 18 weeks of pregnancy. A judge temporarily blocked a law that would have halted most abortions in the state by requiring the procedure to be performed in hospitals. A separate ban on most abortions was indefinitely blocked by a judge in 2022.

Iowa	Ban blocked	22 weeks

An Iowa district court temporarily blocked a ban on abortion after about six weeks of pregnancy. Lawmakers had passed the ban in a single-day special session in July. In June, a deadlocked state Supreme Court kept a nearly identical six-week ban from 2018 permanently blocked.

Montana	Ban blocked	Viability

The Legislature passed 10 anti-abortion laws in 2023, including a ban on the most commonly used procedure in the second trimester. That restriction and several others have been blocked by a court. The Montana Supreme Court has ruled that the state Constitution protects the right to an abortion.

Wyoming	Ban blocked	Viability

A judge in Wyoming temporarily blocked an abortion ban that took effect in March, after a group of health care providers and abortion funds sued to stop it. In June, the same judge temporarily blocked a separate law that explicitly banned the use of abortion pills. A ban on most abortions that was enacted earlier and triggered by the Dobbs decision remains indefinitely blocked.

Alaska	Legal	No gestational limit

The state's Supreme Court has recognized a right to "reproductive choice" under its Constitution.

Kansas	Legal	22 weeks

The state's Supreme Court ruled in 2019 that a pregnant woman's right to personal autonomy is protected in its Constitution, and Kansans voted in August to reject a ballot measure that would have amended the state Constitution to say it contains no right to an abortion. State funds cannot be used to cover the cost of most abortions, and the state has enacted restrictions that limit access to the procedure.

STATE	STATUS OF ABORTION	LEGAL UNTIL
New Hampshire	Legal	24 weeks
Abortion will most likely stay accessible, though it is not expressly protected by state law and state funds cannot be used to cover the cost of most abortions. The state repealed a pre-Roe ban on abortion in 1997.		
Ohio	Legal	22 weeks
Voters enshrined abortion protections in the state Constitution in November 2023. Courts are still deciding how the amendment affects an existing ban on abortion after about six weeks of pregnancy that had been blocked.		
Virginia	Legal	Viability
Abortion will most likely stay accessible, though it is not expressly protected by state law and state funds cannot be used to cover the cost of most abortions. Split control of the state legislature may prevent significant changes until after the next election, in November.		
Wisconsin	Legal	22 weeks
In December, a Wisconsin judge ruled than an 1849 law widely interpreted as an abortion ban did not apply to abortion. Planned Parenthood had already resumed services in all but one location in September, after the judge gave a preliminary ruling. The case may come before the state Supreme Court, which now has a liberal majority.		
Washington, D.C.	Legal with new protections	No gestational limit
Local law protects abortion throughout pregnancy, and a 2023 law shields providers and patients from legal action brought by other jurisdictions. Congress prohibits the use of taxpayer funds to cover the cost of most abortions in the city.		
California	Legal with new protections	Viability
Voters enshrined abortion protections in the state Constitution in November 2022. State law protects abortion, and in earlier in 2022 the governor signed a bill to shield patients and providers from laws in other states.		
Colorado	Legal with new protections	No gestational limit
State law protects abortion, but a 1984 law prohibits using state funds to cover the cost of most abortions. A 2022 executive order and a 2023 law shield those seeking or providing abortions in Colorado from laws in other states.		
Connecticut	Legal with new protections	Viability
State law protects abortion. A law expanding which clinicians can provide abortions took effect in 2022. The law also shields both providers and patients from out-of-state lawsuits.		

STATE	STATUS OF ABORTION	LEGAL UNTIL
Delaware	Legal with new protections	Viability
State law protects abortion, but state funds cannot be used to cover the cost of the procedure. A 2022 law expanded access to providers and shields those seeking or providing abortions in Delaware from laws in other states.		
Hawaii	Legal with new protections	Viability
State law protects abortion, and a new law has expanded access to providers. A 2022 executive order and a 2023 law shield those seeking or providing abortions in Hawaii from laws in other states.		
Illinois	Legal with new protections	Viability
The state's Supreme Court has recognized abortion protections under its Constitution, and state law protects the procedure. A law signed in January shields those seeking or providing abortions in Illinois from laws in other states.		
Maine	Legal with new protections	Viability
State law protects abortion. In 2022, the governor issued an executive order to shield those seeking or providing abortions in Maine from laws in other states. A 2023 law allows an abortion past the point of viability if a doctor decides it is medically necessary.		
Maryland	Legal with new protections	Viability
State law protects abortion, and recent laws have increased access to providers and insurance coverage. A 2023 law shields those seeking or providing abortions in Maryland from laws in other states.		
Massachusetts	Legal with new protections	24 weeks
The Massachusetts Supreme Judicial Court has recognized the right to abortion under its Constitution. A 2022 law shields those seeking or providing abortions in Massachusetts from laws in other states, regardless of the patient's location.		
Michigan	Legal with new protections	Viability
Voters enshrined abortion protections in the state Constitution in November 2022. Earlier that year, the governor issued an executive order to shield those seeking or providing abortions in Michigan from laws in other states.		
Minnesota	Legal with new protections	No gestational limit
The state's Supreme Court has recognized the right to abortion under its Constitution, and in 2023 the state enacted a law to enshrine the right to reproductive care. A 2023 law shields those seeking or providing abortions in Minnesota from laws in other states.		

STATE	STATUS OF ABORTION	LEGAL UNTIL
Nevada	Legal with new protections	24 weeks
State law protects abortion, but state funds cannot be used to cover the cost of most abortions. A 2023 law shields those seeking or providing abortions in Nevada from laws in other states.		
New Jersey	Legal with new protections	No gestational limit
State law protects abortion throughout pregnancy. In 2022, the governor issued an executive order to shield those seeking or providing abortions in New Jersey from laws in other states.		
New Mexico	Legal with new protections	No gestational limit
Abortion will most likely stay accessible, though it is not expressly protected by state law. A 2022 executive order and a 2023 law shield those seeking or providing abortions in New Mexico from laws in other states.		
New York	Legal with new protections	Viability
State law protects abortion. In 2022, the governor signed several bills to shield patients and providers from laws in other states.		
Oregon	Legal with new protections	No gestational limit
State law protects abortion throughout pregnancy. In 2022, the Legislature approved $15 million to support those seeking the procedure.		
Pennsylvania	Legal with new protections	24 weeks
Abortion will most likely stay accessible, though it is not expressly protected by state law and state funds cannot be used to cover the cost of most abortions. In 2022, the governor issued an executive order that shields those seeking or providing abortions in Pennsylvania from laws in other states.		
Rhode Island	Legal with new protections	Viability
State law protects abortion, but state funds cannot be used to cover the cost of most abortions. In 2022, the governor issued an executive order to shield those seeking or providing abortions in Rhode Island from laws in other states.		
Vermont	Legal with new protections	No gestational limit
Voters enshrined abortion protections in the state Constitution in November 2022. State law also protects abortion throughout pregnancy. Two 2023 laws shield those seeking or providing abortions in Vermont from laws in other states, and they include protection for those using medication abortion.		

STATE	STATUS OF ABORTION	LEGAL UNTIL
Washington	Legal with new protections	Viability

State law protects abortion, and recent laws have expanded access to providers. A 2023 law shields those seeking or providing abortions in Washington from laws in other states.

Note: Weeks of pregnancy are counted since the last menstrual period.

By Allison McCann, Amy Schoenfeld Walker, Ava Sasani, Taylor Johnston, Larry Buchanan and Jon Huang. Additional reporting by Margot Sanger-Katz and Kate Zernike.

Correction: June 24, 2022
An earlier version of this article misstated the legal status of abortion in Utah. As of 4 p.m. on June 24, the state attorney general had issued a statement saying the state's abortion ban had been triggered, but it had not yet been authorized by the legislature's general counsel. By 8:30 p.m., the counsel authorized the ban and it went into effect.

Correction: June 28, 2022
A table in an earlier version of this article misstated which abortion ban is being challenged in Texas state court. Abortion rights supporters are challenging a pre-Roe ban, not the state's trigger ban.

Correction: Aug. 2, 2023
An earlier version of this article referred incorrectly to the legal status of abortion in Indiana. While Indiana abortion providers stopped offering abortion services in anticipation of an abortion ban taking effect on Aug. 1, the law did not take effect.

Exhibit 7

FDA Risk Evaluation and Mitigation Strategy (REMS) Public Dashboard

Total REMS | Active REMS | ETASU | Shared REMS | Modifications | REMS Revisions | REMS Released | REMS Summary | Disclaimer | User Manual | FAQ | Site Feedback

Ever Approved
312

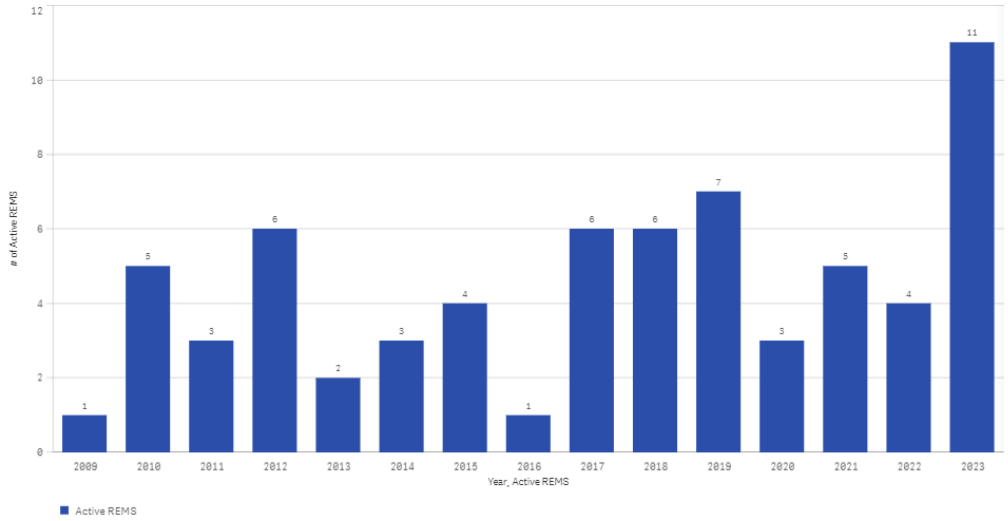
User Selection
-NA-

Currently Active
67

Yearly | Quarterly | Monthly

Active REMS

Currently Active REMS



Currently Active REMS

Name	Application ...	REMS ...	Lates...	El...	Com...	Medic...	REMS Materials	R...	Curre...
Abecma	BLA #125736	03/26/2021	04/20/2021	Yes	No	No	Click here	406	Yes
Adasuve	NDA #022549	12/21/2012	01/27/2022	Yes	No	No	Click here	2	Yes
Addyi	NDA #022526	08/18/2015	10/09/2019	No	No	Yes	Click here	350	Yes
Alvimopan Shared S...	Multiple Applicati...	12/19/2019	06/12/2023	Yes	No	No	Click here	397	Yes
Ambrisentan Share...	Multiple Applicati...	03/28/2019	06/08/2021	Yes	No	No	Click here	396	Yes
Aveed	NDA #022219	03/05/2014	05/26/2022	Yes	No	No	Click here	313	Yes
Bosentan	Multiple Applicati...	04/26/2019	04/29/2022	Yes	No	No	Click here	395	Yes
Breyanzi	BLA #125714	02/05/2021	06/24/2022	Yes	No	No	Click here	405	Yes
Brixadi	NDA #210136	05/23/2023	05/23/2023	Yes	No	No	Click here	418	Yes
Buprenorphine Tran...	Multiple Applicati...	02/22/2013	12/16/2022	Yes	No	Yes	Click here	9	Yes
Camzyos	NDA #214998	04/28/2022	12/19/2023	Yes	No	No	Click here	413	Yes
Caprelsa	NDA #022405	04/06/2011	01/05/2024	Yes	No	No	Click here	11	Yes
Carvykti	BLA #125746	02/28/2022	05/18/2023	Yes	No	No	Click here	412	Yes
Clozapine	Multiple Applicati...	09/15/2015	09/29/2023	Yes	No	No	Click here	351	Yes
Copiktra	NDA #211155	09/24/2018	02/02/2022	No	Yes	No	Click here	382	Yes
Dsuvia	NDA #209128	11/02/2018	12/19/2023	Yes	No	No	Click here	384	Yes
Elrexfio	BLA #761345	08/14/2023	12/13/2023	Yes	Yes	No	Click here	421	Yes
Empaveli	NDA #215014	05/14/2021	05/14/2021	Yes	No	No	Click here	409	Yes
Fabhalta	NDA #218276	12/05/2023	12/05/2023	Yes	No	No	Click here	425	Yes
Filspari	NDA #216403	02/17/2023	12/20/2023	Yes	No	No	Click here	416	Yes
Fintepla	NDA #212102	06/25/2020	05/30/2023	Yes	Yes	No	Click here	400	Yes
Gattex	NDA #203441	12/21/2012	10/21/2022	Yes	No	No	Click here	21	Yes
Hepzato	NDA #201848	08/14/2023	01/22/2024	Yes	No	No	Click here	422	Yes
Isotretinoin iPLEDGE	Multiple Applicati...	10/22/2010	10/03/2023	Yes	No	No	Click here	24	Yes
Juxtapid	NDA #203858	12/21/2012	06/16/2022	Yes	No	No	Click here	25	Yes

Data as of February 5, 2024

This page displays the currently approved REMS. The graph and table display the number of REMS approved in a given time period that are still active today. The elements of the REMS reflected in the table are the latest elements of the REMS not the elements with which the REMS was initially approved.

https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/6840df68-c772-45f1-bc4f-39d8b04cbfc1/state/analysis

Name	Application Number	REMS Approved Date	Latest Version Date	Elements to Assure Safe Use	Communication Plan	Medication Guide	REMS Materials	REMS ID	Currently Approved
Abecma	BLA #125736	03/26/2021	04/20/2021	Yes	No	No	Click here	406	Yes
Adasuve	NDA #022549	12/21/2012	01/27/2022	Yes	No	No	Click here	2	Yes
Addyi	NDA #022526	08/18/2015	10/09/2019	No	No	Yes	Click here	350	Yes
Alvimopan Shared System REMS	Multiple Applications	12/19/2019	06/12/2023	Yes	No	No	Click here	397	Yes
Ambrisentan Shared System	Multiple Applications	03/28/2019	06/08/2021	Yes	No	No	Click here	396	Yes
Aveed	NDA #022219	03/05/2014	05/26/2022	Yes	No	No	Click here	313	Yes
Bosentan	Multiple Applications	04/26/2019	04/29/2022	Yes	No	No	Click here	395	Yes
Breyanzi	BLA #125714	02/05/2021	06/24/2022	Yes	No	No	Click here	405	Yes
Brixadi	NDA #210136	05/23/2023	05/23/2023	Yes	No	No	Click here	418	Yes
Buprenorphine Transmucosal Products for Opioid Dependence (BTOD)	Multiple Applications	02/22/2013	12/16/2022	Yes	No	Yes	Click here	9	Yes
Camzyos	NDA #214998	04/28/2022	12/19/2023	Yes	No	No	Click here	413	Yes
Caprelsa	NDA #022405	04/06/2011	01/05/2024	Yes	No	No	Click here	11	Yes
Carvykti	BLA #125746	02/28/2022	05/18/2023	Yes	No	No	Click here	412	Yes
Clozapine	Multiple Applications	09/15/2015	09/29/2023	Yes	No	No	Click here	351	Yes
Copiktra	NDA #211155	09/24/2018	02/02/2022	No	Yes	No	Click here	382	Yes
Dsuvia	NDA #209128	11/02/2018	12/19/2023	Yes	No	No	Click here	384	Yes
Elrexfio	BLA #761345	08/14/2023	12/13/2023	Yes	Yes	No	Click here	421	Yes
Empaveli	NDA #215014	05/14/2021	05/14/2021	Yes	No	No	Click here	409	Yes
Fabhalta	NDA #218276	12/05/2023	12/05/2023	Yes	No	No	Click here	425	Yes
Filspari	NDA #216403	02/17/2023	12/20/2023	Yes	No	No	Click here	416	Yes
Fintepla	NDA #212102	06/25/2020	05/30/2023	Yes	Yes	No	Click here	400	Yes
Gattex	NDA #203441	12/21/2012	10/21/2022	Yes	No	No	Click here	21	Yes
Hepzato	NDA #201848	08/14/2023	01/22/2024	Yes	No	No	Click here	422	Yes
Isotretinoin iPLEDGE	Multiple Applications	10/22/2010	10/03/2023	Yes	No	No	Click here	24	Yes
Juxtapid	NDA #203858	12/21/2012	06/16/2022	Yes	No	No	Click here	25	Yes
Jynarque	NDA #204441	04/23/2018	09/29/2023	Yes	Yes	No	Click here	380	Yes
Kymriah	BLA #125646	08/30/2017	05/27/2022	Yes	No	No	Click here	368	Yes
Lemtrada	BLA #103948	11/14/2014	12/15/2023	Yes	No	No	Click here	340	Yes
Lenalidomide	Multiple Applications	05/21/2021	03/24/2023	Yes	No	No	Click here	410	Yes
Lumryz	NDA #214755	05/01/2023	10/31/2023	Yes	No	No	Click here	401	Yes
Macitentan	Multiple Applications	04/06/2021	02/01/2023	Yes	No	No	Click here	407	Yes
Mifepristone	Multiple Applications	04/11/2019	03/23/2023	Yes	No	No	Click here	390	Yes
Myalept	BLA #125390	02/24/2014	03/31/2023	Yes	No	No	Click here	314	Yes
Mycophenolate	Multiple Applications	09/25/2012	10/03/2023	Yes	No	No	Click here	37	Yes
Natpara	BLA #125511	01/23/2015	09/14/2023	Yes	No	No	Click here	343	Yes
Opioid Analgesic REMS	Multiple Applications	07/09/2012	04/09/2021	Yes	No	Yes	Click here	17	Yes
Palforzia	BLA #125696	01/31/2020	05/26/2021	Yes	No	No	Click here	398	Yes
Palynziq	BLA #761079	05/24/2018	12/09/2023	Yes	No	No	Click here	381	Yes
Pomalidomide	Multiple Applications	10/30/2020	10/30/2020	Yes	No	No	Click here	404	Yes
Pomalyst	NDA #204026	02/08/2013	03/24/2023	Yes	No	No	Click here	41	Yes
Probuphine	NDA #204442	05/26/2016	11/01/2018	Yes	No	Yes	Click here	356	Yes
Prolia	BLA #125320	06/01/2010	01/19/2024	No	Yes	Yes	Click here	43	Yes
PS-Mycophenolate	Multiple Applications	06/01/2023	06/01/2023	Yes	No	No	Click here	419	Yes
Qsymia	NDA #022580	07/17/2012	05/09/2023	Yes	No	Yes	Click here	45	Yes
Riociguat Shared System REMS	Multiple Applications	09/01/2022	09/01/2022	Yes	No	No	Click here	414	Yes
Siliq	BLA #761032	02/15/2017	07/19/2023	Yes	No	No	Click here	362	Yes
Sodium Oxybate	ANDA #202090	01/17/2017	01/17/2024	Yes	No	No	Click here	361	Yes
Soliris	BLA #125166	06/04/2010	04/07/2020	Yes	No	No	Click here	49	Yes
Spravato	NDA #211243	03/05/2019	01/03/2022	Yes	No	No	Click here	386	Yes
Sublocade	NDA #209819	11/30/2017	07/03/2023	Yes	No	No	Click here	376	Yes
Tecvayli and Talvey	Multiple Applications	10/25/2022	11/16/2023	Yes	Yes	No	Click here	415	Yes
Tegsedi	NDA #211172	10/05/2018	08/24/2023	Yes	No	No	Click here	383	Yes
Thalidomide	ANDA #213267	04/27/2023	04/27/2023	Yes	No	No	Click here	417	Yes
Thalomid	NDA #020785	08/03/2010	03/24/2023	Yes	No	No	Click here	58	Yes
Transmucosal Immediate-Release Fentanyl (TIRF) Products	Multiple Applications	12/28/2011	12/08/2022	Yes	No	Yes	Click here	60	Yes
Turalio	NDA #211810	08/02/2019	04/17/2023	Yes	Yes	No	Click here	389	Yes
Tyruko	BLA #761322	08/24/2023	08/24/2023	Yes	No	Yes	Click here	423	Yes
Tysabri	BLA #125104	10/07/2011	09/01/2023	Yes	No	Yes	Click here	63	Yes
Ultomiris	BLA #761108	12/21/2018	08/03/2022	Yes	No	No	Click here	385	Yes
Vanflyta	NDA #216993	07/20/2023	07/20/2023	Yes	No	No	Click here	420	Yes
Vigabatrin	Multiple Applications	04/27/2017	10/12/2022	Yes	No	No	Click here	364	Yes
Xiaflex	BLA #125338	02/02/2010	11/02/2022	Yes	No	No	Click here	71	Yes
Xywav and Xyrem	Multiple Applications	02/27/2015	01/16/2024	Yes	No	No	Click here	345	Yes
Yescarta and Tecartus	Multiple Applications	10/18/2017	04/01/2022	Yes	No	No	Click here	375	Yes
Zilbrysq	NDA #216834	10/17/2023	01/16/2024	Yes	No	No	Click here	424	Yes
Zulresso	NDA #211371	03/19/2019	10/17/2023	Yes	No	No	Click here	387	Yes
Zyprexa Relprevv	NDA #022173	12/11/2009	04/28/2021	Yes	Yes	Yes	Click here	74	Yes

Exhibit 8

Opioid Regulations: State by State Guide

This guide has been created for the purpose of providing practical, state specific information for emergency physicians that prescribe opioid medications in an emergency department setting. Because it is specific to emergency physicians and departments, it does not include requirements related to other areas of medical practice.

This guide will provide the following information for each state:

- PDMP mandates
- Accessibility by delegates of the physician in order to comply with those requirements.
- CME mandates specific to opioid related issues (pain management, addiction, PDMP, etc.)
- Community availability of naloxone and suboxone
- Limitations on days' supply of a prescription originating in the emergency department
- Availability of community treatment resources

This information is accurate as of January 2021. It is provided for informational purposes only and should not be construed as legal advice. Consulting actual statutes and regulations may be necessary.

Alabama
Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
District of Columbia
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Kentucky
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Mississippi
Missouri
Montana
Nebraska
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Carolina
North Dakota
Ohio
Oklahoma
Oregon
Pennsylvania
Rhode Island
South Carolina
South Dakota
Tennessee
Texas
Utah
Vermont
Virginia
Washington
West Virginia
Wisconsin
Wyoming

Opioid Response Network

Funding for this initiative was made possible (in part) by grant no. 1H79TI083343 from SAMHSA.

ALABAMA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The RMS rule requires the following:

- For 30 MME or less per day, use PDMP in a manner consistent with good clinical practice
- For more than 30 MME per day, review PDMP at least two times per year and document use of REMS in medical record
- For more than 90 MME per day*, review PDMP every time prescriptions are written, on the same day the prescriptions are written, and document use of REMs in medical record
  *Cumulative of all prescriptions written on the same day

Exemptions

The rule exempts the PDMP query requirements for controlled substances prescriptions written for:

- Nursing home patients
- Hospice patients, where the prescription indicates hospice on the physical prescription
- Treatment of active, malignant pain*, or
- Intra-operative care**
- In-hospital (in-patient orders) prescribing (PDMP query rule does apply to prescriptions written at discharge)

PDMP DELEGATE ACCESSIBILITY

A licensed physician approved by the department who has authority to prescribe, dispense, or administer controlled substances may designate up to two employees who may access the database on the physician's behalf.

A licensed certified registered nurse practitioner or a licensed certified nurse midwife approved by the department who is authorized to prescribe, administer, or dispense pursuant to a Qualified Alabama Controlled Substances Registration Certificate; provided, however, that access shall be limited to information concerning a current or prospective patient of the certified registered nurse practitioner or certified nurse midwife.

A licensed assistant to physician approved by the department who is authorized to prescribe, administer, or dispense pursuant to a Qualified Alabama Controlled Substances Registration Certificate; provided, however, that access shall be limited to information concerning a current patient of the assistant to the physician or an individual seeking treatment from the assistant to physician.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

All Controlled Substance Certificate holders must complete 2 Category 1 CME hours every 2 years in the area of controlled substance prescribing practices, recognizing signs of misuse or abuse, or controlled substance prescribing for chronic pain.

NALOXONE AND SUBOXONE AVAILABILITY

HB208 was signed into law in 2015 and provided immunity for prescribing and administering an opioid antagonist, such as naloxone. In 2016, HB379 was signed into law, providing the State Health Officer or a county health officer the authority to write a standing order for dispensing naloxone.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Alabama Department of Mental Health provides a list of treatment and prevention providers on their website: http://www.mh.alabama.gov/SA/?sm=d. The Prescription Drug Monitoring Program website also provides resources (http://www.adph.org/PDMP/Default.asp?id=1417)

ALASKA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The requirement to review the database is not applicable to a practitioner dispensing, prescribing, or administering a controlled substance to a person receiving treatment in an emergency room or at the scene of an emergency or in an ambulance.

PDMP DELEGATE ACCESSIBILITY

A licensed practitioner having authority to prescribe controlled substances or an agent or employee of the practitioner whom the practitioner has authorized to access the database on the practitioner's behalf, to the extent the information relates specifically to a current patient of the practitioner to whom the practitioner is prescribing or considering prescribing a controlled substance; the agent or employee must be licensed or registered under AS 08;

CME REQUIREMENTS FOR OPIOID PRESCRIBING

A holder of a DEA number must complete at least 2 hours in pain management, opioid use, and addiction.

NALOXONE AND SUBOXONE AVAILABILITY

Under the authority of AS 17.20.085 and a February 14, 2017 Declaration of Disaster Emergency, a **medical standing order** authorizes any approved Department of Health and Social Services Project HOPE Overdose Response Program (ORP) to maintain supplies of opioid overdose rescue kits for the purpose of distributing/administering to a person at risk of experiencing an opioid overdose or a family member, friend, caregiver, or other person in a position to administer the opioid overdose drug naloxone (i.e., Narcan ® Nasal Spray) to a person at risk of experiencing an opioid overdose.

LIMITATIONS ON DAYS' SUPPLY

7 days for an initial prescription. Exceptions must be documented if the physician's professional judgement deems it appropriate for chronic pain management or if the patient is unable to access a practitioner for a refill.

AVAILABILITY OF TREATMENT RESOURCES: The state maintains a list of treatment providers here: http://dhss.alaska.gov/dbh/Documents/TreatmentRecovery/SUD%20Providers/Substance%20Use%20Disorder%20Treatment%20Providers.pdf

According to the state's website, many of those listed accept Medicaid patients.

ARIZONA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

All prescribers are required to obtain a patient utilization report from the Controlled Substances Prescription Monitoring Program (PMP) prior to prescribing an opioid analgesic or benzodiazepine controlled substance.

PDMP DELEGATE ACCESSIBILITY

The board may release data collected by the program to a person who is authorized to prescribe or dispense a controlled substance, or a delegate who is authorized by the prescriber or dispenser, to assist that person to provide medical or pharmaceutical care to a patient or to evaluate a patient.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Holders of a DEA number who are renewing their licenses must complete at least 3 hours of opioid, substance use disorder, or addiction related CME each renewal cycle.

NALOXONE AND SUBOXONE AVAILABILITY

The standing order issued by the Director of Arizona DHS authorizes any Arizona-licensed pharmacist to dispense naloxone to any individual in accordance with the conditions of the order. The current standing order expires 11/1/22.

LIMITATIONS ON DAYS' SUPPLY

Initial prescriptions are limited to a five day supply, with the following exceptions if the patient:

- Has an active oncology diagnosis
- Has a traumatic injury, not including a surgical procedure
- Is receiving hospice, palliative, or end of life care
- Is receiving skilled nursing facility care
- Is receiving treatment for burns
- Is receiving MAT for a substance abuse disorder
- Is an infant being weaned off opioids at the time of discharge.

New prescriptions may also not be greater than 90 morphine equivalents, with the same exceptions other than the one involving infants. Additional exceptions require consultation with a physician certified in pain and must be accompanied by a naloxone or similar prescription.

AVAILABILITY OF TREATMENT RESOURCES: Information regarding community-based programs can be found here: https://www.azpreventionresource.com/

ARKANSAS

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Checking the PDMP is required when prescribing a Schedule II or III opioid for every time prescribing the medication to the patient; and a benzodiazepine for the first time prescribing the medication to the patient. This does not apply to a palliative care or hospice patient.

PDMP DELEGATE ACCESSIBILITY

The Arkansas Department of Health grants access of the Arkansas PDMP database to authorized users such at prescribers (physician, nurse practitioner, dentist, etc.), pharmacists, delegates of prescribers/pharmacists, professional licensing boards, and certified law enforcement prescription drug diversion investigators.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

Arkansas Governor Asa Hutchinson has a standing order allowing Arkansas-licensed pharmacists to initiate naloxone therapy including ordering, dispensing and/or administering naloxone, along with any necessary supplies for administration, to eligible persons who are at risk of experiencing an opioid-related overdose, or who are family members, friends, or others who are in a position to assist a person at risk of experiencing an opioid-related overdose.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES

The state's lists of substance abuse resources can be found here:

- https://www.arkansaspmp.com/substance-abuse-resources.html
- https://www.artakeback.org/substance-abuse-treatment/

CALIFORNIA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A health care practitioner in the emergency department of an acute care hospital is exempt from the requirement to review the database if the controlled substance does not exceed a non-refillable seven-day supply.

PDMP DELEGATE ACCESSIBILITY

The database can be accessed by practitioners eligible to prescribe controlled substances, pharmacists authorized to dispense controlled substances, sworn law enforcement personnel, and authorized regulatory boards.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Within 4 yours or by their second license date, physicians must complete 12 units on pain management and treatment of the terminally ill. As an alternative, the physician may complete a 1-time CE course of 12 hours in the treatment and management of opioid-dependent patients, including 8 hours of training in buprenorphine or similar treatment by the next licensure renewal date.

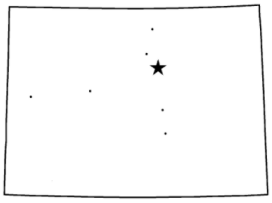
NALOXONE AND SUBOXONE AVAILABILITY

AB 2760 (Wood, Chapter 324) was signed into law in 2018 and became effective on January 1, 2019. This bill requires prescribers to offer a prescription for naloxone hydrochloride or another drug approved by the United States Food and Drug Administration for the complete or partial reversal of opioid depression to a patient when certain conditions (more than 90 MME per day, opioid prescribed concurrently with a benzodiazepine, or the patient presents with increased risk of overdose) are present. This bill also requires a prescriber, consistent with the existing standard of care, to provide education to a patient and his or her designee, or if the patient is a minor, to the patient's parent or guardian, on overdose prevention and the use of naloxone or other similar drug approved by the FDA.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The state maintains a directory of substance use disorder services here: https://www.dhcs.ca.gov/provgovpart/Pages/sud-directories.aspx

COLORADO



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prescribers and dispensers should access the PDMP and review the patient profile prior to making a determination regarding the initiation of opioid therapy. Prescribers and dispensers should also review the patient's PDMP profile prior to each instance in which opioids are prescribed, refilled or dispensed. Prescribers and Dispensers may want to consider reviewing the patient's pet or animal profile if there is a concern for diversion of veterinary prescriptions.

PDMP DELEGATE ACCESSIBILITY

A prescriber can authorize up to three delegates to access the PDMP for his/her patients.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Licensees must complete at least 2 hours per licensing cycle related to best practices for opioid prescribing, recognition of substance use disorders, referral of patients with SUDs for treatment, and use of the PDMP. Those with a national board certification requiring equivalent substance use prevention training are exempted, as area those who attest in writing that they do not prescribe opioids.

NALOXONE AND SUBOXONE AVAILABILITY

The CMO of the Colorado Department of Public Health may issue standing orders to specified agencies upon request. Information about the program can be found here: https://cdphe.colorado.gov/prevention-and-wellness/injury-prevention/opioid-overdose-prevention/naloxone-standing-orders

LIMITATIONS ON DAYS' SUPPLY

With specified exceptions, a physician or physician assistant shall not prescribe more than a 7-day supply of an opioid to a patient who has not had an opioid prescription in the last 12 months from that physician or physician assistant. The physician or physician assistant may exercise discretion to include a second fill for a 7-day supply.

AVAILABILITY OF TREATMENT RESOURCES: The Colorado Consortium for Prescription Drug Abuse Prevention has a work group devoted to identifying gaps and needs with regard to treatment programs in the state. Information about this work group can be found here: https://corxconsortium.org/work-groups/treatment/

CONNECTICUT

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Whenever a prescribing practitioner prescribes greater than a 72-hour supply of any *Schedule V* controlled substance for the treatment of any patient, such prescriber, or such prescriber's authorized agent, shall review, not less than annually, the patient's records in the CPMRS.

PDMP DELEGATE ACCESSIBILITY

Practitioner's authorized agent, licensed or unlicensed, may register for their own CPMRS user account.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

By the time of the first renewal period for which CME is mandated and every 6 years thereafter, at least 1 hour is required in prescribing controlled substances and pain management.

NALOXONE AND SUBOXONE AVAILABILITY

- A primary care provider/family doctor can give a prescription for naloxone that can be filled at any CT pharmacy.
- Any provider who is able to prescribe an opioid can prescribe naloxone.
- Pharmacists in CT who have completed training to become certified can both prescribe and dispense naloxone.
- DMHAS-funded Regional Behavioral Health Action Organizations (RBHAOs) can provide training as well as naloxone.
- DPH-supported mobile vans offering Specialized Syringe Programs for needle exchange that also offer naloxone and training.
- Harm Reduction programs may also offer free naloxone and training.

LIMITATIONS ON DAYS' SUPPLY

- limit Rx to 7 days for 1st time Rx to adults
- limit Rx to 5 days for all Rx to minors
- if in professional medical judgment of a practitioner, more than a seven-day supply of an opiate is required, then the practitioner may issue a prescription for the quantity needed and rationale must be documented

AVAILABILITY OF TREATMENT RESOURCES: The state maintains information about treatment resources here: https://public.tableau.com/views/CTBHPMedicaidMATProviderMap/TreatmentProviders/?:showVizHome=no

DELAWARE

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescriber, or other person authorized by the prescriber, shall obtain, before writing a prescription for a controlled substance listed in Schedule II, III, IV or V for a patient, a patient utilization report regarding the patient for the preceding 12 months from the computerized program established by the Office of Controlled Substances when the prescriber has a reasonable belief that the patient may be seeking the controlled substance, in whole or in part, for any reason other than the treatment of an existing medical condition. The prescriber shall review the patient utilization report to assess whether the prescription for the controlled substance is necessary.

PDMP DELEGATE ACCESSIBILITY

The Office of Controlled Substances may provide data in the prescription monitoring program in the form of a report to a prescriber, or other person authorized by the prescriber, or a dispenser, or other person authorized by the dispenser, who requests information and certifies that the requested information is for the purpose of providing medical or pharmaceutical treatment to a bona fide patient.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

A physician must complete 2 hours of CE every 2 years in controlled substance prescribing practices, treatment of chronic pain, or related subjects.

NALOXONE AND SUBOXONE AVAILABILITY

Mail-order naloxone is available through a Memorandum of Understanding between DHSS and the New York-based harm-reduction nonprofit NEXT Distro. Delawareans who want to place a mail order for naloxone should visit the “Overdose Prevention” page on HelpIsHereDE.com and access NEXT Distro’s Delaware program. Customers must watch a video, take a short quiz, and complete a request form. DPH will receive the request from NEXT Distro’s virtual platform and will mail individuals free naloxone. People will receive their naloxone within a few days. All contact information will be kept confidential. Delawareans can still obtain Narcan or naloxone without a prescription at pharmacies, and Narcan at overdose prevention trainings and naloxone distribution events.

LIMITATIONS ON DAYS’ SUPPLY

- limit Rx to 7 days for 1st time Rx to adults
- limit Rx to 7 days for all Rx to minors
- if in professional medical judgment of a practitioner, more than a seven-day supply of an opiate is required, then the practitioner may issue a prescription for the quantity needed and rationale must be documented

AVAILABILITY OF TREATMENT RESOURCES: The state maintains information regarding treatment resources here: https://www.helpisherede.com/Get-Help?source=homepage-link#help-now

DISTRICT OF COLUMBIA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Currently, prescribers and dispensers who are licensed in DC are only required to register with the PDMP. There is no mandate to query (check) the PDMP; however, legislation is pending.

PDMP DELEGATE ACCESSIBILITY

Physicians, pharmacists, nurse practitioners, physician assistants, dentists, veterinarians, optometrists, podiatrists, naturopathic physicians, and other licensed professionals authorized by DC Health can access PDMP data. A prescriber may delegate authority to access data to up to 2 licensed, registered, or certified health care professionals who are employed at the same location under the direct supervision of the prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

Residents can text LiveLongDC to 888-111 to get information on where they can access free naloxone kits across the District.

LIMITATIONS ON DAYS' SUPPLY

Prescription limited to 7-day supply

AVAILABILITY OF TREATMENT RESOURCES: The DC Department of Behavioral Health offers a full range of prevention, treatment, and recovery services. Call the 24 hour Access Helpline at 1-(888)-793-4357 (7WE-HELP) to enroll or get more information.

FLORIDA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescriber or dispenser or a designee of a prescriber or dispenser must consult the system to review a patient's controlled substance dispensing history before prescribing or dispensing a controlled substance for a patient age 16 or older. The requirement does not apply to a Schedule V.

PDMP DELEGATE ACCESSIBILITY

"Designee" means a person, preferably a licensed or certified health care professional, appointed to act as an agent of a prescriber or dispenser for the purposes of requesting or receiving information from the Prescription Drug Monitoring Program database, E-FORCSE®. The designee must register with the program.

The following persons must be provided direct access to information in the system:

(a) A prescriber or dispenser or his or her designee.

(b) An employee of the United States Department of Veterans Affairs, the United States Department of Defense, or the Indian Health Service who provides health care services pursuant to such employment and who has the authority to prescribe or dispense controlled substances shall have access to the information in the program's system upon verification of employment.

(c) The program manager or designated program and support staff to administer the system

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Every person registered with the DEA and authorized to prescribe controlled substances must complete 2 hours of AMA Category 1 or AOA Category 1-A on prescribing controlled substances for each 2 years.

NALOXONE AND SUBOXONE AVAILABILITY

(3) An authorized health care practitioner may prescribe and dispense an emergency opioid antagonist to a patient or caregiver for use in accordance with this section, and pharmacists may dispense an emergency opioid antagonist pursuant to such a prescription or pursuant to a non-patient-specific standing order for an autoinjection delivery system or intranasal application delivery system, which must be appropriately labeled with instructions for use. Such patient or caregiver is authorized to store and possess approved emergency opioid antagonists and, in an emergency situation when a physician is not immediately available, administer the emergency opioid antagonist to a person believed in good faith to

be experiencing an opioid overdose, regardless of whether that person has a prescription for an emergency opioid antagonist.

(4) The following persons are authorized to possess, store, and administer emergency opioid antagonists as clinically indicated:

(a) Emergency responders, including, but not limited to, law enforcement officers, paramedics, and emergency medical technicians.

(b) Crime laboratory personnel for the statewide criminal analysis laboratory system as described in s. 943.32, including, but not limited to, analysts, evidence intake personnel, and their supervisors.

(5) A person, including, but not limited to, an authorized health care practitioner, a dispensing health care practitioner, or a pharmacist, who possesses, administers, prescribes, dispenses, or stores an approved emergency opioid antagonist in compliance with this section and s. 768.13 is afforded the civil liability immunity protections provided under s. 768.13.

(6)(a) An authorized health care practitioner, acting in good faith and exercising reasonable care, is not subject to discipline or other adverse action under any professional licensure statute or rule and is immune from any civil or criminal liability as a result of prescribing an emergency opioid antagonist in accordance with this section.

(b) A dispensing health care practitioner or pharmacist, acting in good faith and exercising reasonable care, is not subject to discipline or other adverse action under any professional licensure statute or rule and is immune from any civil or criminal liability as a result of dispensing an emergency opioid antagonist in accordance with this section.

LIMITATIONS ON DAYS' SUPPLY

3 days for acute pain. 7-day supply permitted if medically necessary based on provider professional judgment. Definition of acute pain excludes: cancer, terminal conditions, traumatic injury, and palliative care. Exceptions in dispensing provisions allow for MAT

AVAILABILITY OF TREATMENT RESOURCES: The state maintains information regarding treatment resources here: https://www.myflfamilies.com/service-programs/samh/substance-abuse.shtml

GEORGIA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescriber is required to check the PDMP before writing a prescription for the first time for:

1. Benzodiazepines
2. Opiate drugs or cocaine derivatives listed in Schedule II

Thereafter, if the prescription continues, the prescriber should check the PDMP at least every 90 days.

The prescriber is not required to check the PDMP in these four situations:

- If the prescription is for no more than a three-day supply and no more than 26 pills
- If the patient is in a health care facility, such as a hospital, nursing home, intermediate care home, personal care home or hospice, which provides patient care and prescriptions to be administered to the patient on the premises
- If the patient has had outpatient surgery at a hospital or ambulatory surgical center and the prescription is for no more than a 10-day supply and no more than 40 pills
- If the patient is receiving treatment for cancer

PDMP DELEGATE ACCESSIBILITY

A prescriber approved for PDMP access may designate up to 2 persons per shift or rotation to access the PDMP on his/her behalf as delegates if the persons are employed by the emergency department in which the prescriber practices and are approved by the hospital medical director.

The delegates must hold a current license as a physician or physician assistant, not have been convicted of a felony or criminal offense involving illegal drug use, possession, or trafficking, and must have passed a required online training course, received instruction in the dispenser's PDMP policies, and must have signed a Responsibility Statement.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Each licensee with DEA registration who prescribes controlled substances must complete prior to license renewal 3 hours of Category 1 CME on responsible opioid prescribing. The Board may accept ABMS, AOA, or Royal Colleges (Canada) certification in lieu of CME requirements.

NALOXONE AND SUBOXONE AVAILABILITY

The Commissioner of Public Health has issued a standing Order permitting licensed pharmacies to dispense naloxone to eligible persons or entities. Eligible persons or entities include “family members, friends, co-workers, first responders, schools, pain management clinics, harm reduction organizations, and any other persons or entities ("Eligible Persons or Entities") are in a position to provide assistance to a person experiencing an opioid-related overdose through the timely administration of the opioid antagonist naloxone.”

LIMITATIONS ON DAYS’ SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Georgia Department of Behavioral Health and Developmental Disabilities maintains a list of organizations that can help find resources here: https://dbhdd.georgia.gov/additional-resources

HAWAII

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The PDMP information must be considered prior to prescribing a Schedule II, III, or IV controlled substance. This requirement does not apply for a prescription of 3 days or less made in an emergency situation, by an emergency medical provider, or in an emergency room.

PDMP DELEGATE ACCESSIBILITY

Delegates that a prescriber authorizes to preform PDMP checks are allowed to register for their own account in the PDMP. If a staff member from your office (i.e. office manager) signs up as a delegate, there is a dual approval process. An email will be sent to you as their Supervisor to approve their account as well as approval by the PDMP Administrator.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

A pharmacist may prescribe and dispense an opioid antagonist to an individual who is at risk for an opioid overdose or a family member or caregiver of an individual who is at risk of an opioid overdose regardless of whether the individual has evidence of a previous prescription for an opioid antagonist from a practitioner authorized to prescribe opioids.

LIMITATIONS ON DAYS' SUPPLY

Opioids limited to 30 days. Initial concurrent prescriptions for opioids and benzodiazepines ust not be for longer than 7 days unless deemed necessary for the treatment of:

(1) Pain experienced while the patient is in post-operative care;
(2) Chronic pain and pain management;
(3) Substance abuse or opioid or opiate dependence;
(4) Cancer;
(5) Pain experienced while the patient is in palliative care; or
(6) Pain experienced while the patient is in hospice care;

AVAILABILITY OF TREATMENT RESOURCES: The Hawaii Department of Health, Alcohol and Drug Abuse Division maintains a list of treatment resources here: https://health.hawaii.gov/substance-abuse/prevention-treatment/treatment/treatment-services/

IDAHO

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Generally, a prescriber is required to check the database prior to issuing a prescription for outpatient us for an opioid analgesic or benzodiazepine listed in schedule II, III, or IV. There is an exception when the prescription is in a quantity intended to last no more than 3 days.

PDMP DELEGATE ACCESSIBILITY

A practitioner, licensed in Idaho or another state, having authority to prescribe controlled substances, or a delegate under the practitioner's supervision, to the extent the information relates specifically to a current patient of the practitioner to whom the practitioner is prescribing or considering prescribing any controlled substance.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

Idaho's law allows pharmacists and other health professionals to prescribe and dispense to anyone at risk for an opioid-related overdose or to anyone who may encounter an such an individual. The Office of Drug Policy has a standing order to obtain naloxone on behalf of eligible agencies. These agencies will then be equipped to administer naloxone and keep an overdose patient alive until they can be transported to an emergency department. The agencies may also distribute the naloxone to individuals at risk of overdose, as well as their friends and family.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The state maintains a list of statewide crisis centers here: https://healthandwelfare.idaho.gov/services-programs/behavioral-health/statewide-crisis-centers

ILLINOIS

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The requirement to access the PDMP does not apply to a 7-day or less supply provided by an emergency department treating an acute, traumatic medical condition.

PDMP DELEGATE ACCESSIBILITY

Only the following licensed healthcare professionals shall serve as an authorized designee for a prescriber or dispenser for office or pharmacy practice sites:

- registered nurse;
- licensed practical nurse;
- pharmacy technician;
- student pharmacist; or
- certified medical assistant.

The prescriber or dispenser shall only have up to three designees.
The prescriber and dispenser shall register the designees and must also agree to the terms and conditions for designees.
Each designee shall have an individual account that must be linked to the prescriber or dispenser.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Physicians must take 3 hours of safe opioid prescribing practices offered or accredited by a professional association, or state or federal government agency. Hours taken in another state or for board certification can also meet this requirement.

NALOXONE AND SUBOXONE AVAILABILITY

The Naloxone Standing Order authorizes trained, licensed pharmacists and overdose education and naloxone distribution (OEND) programs to provide naloxone to individuals who request it to reverse a potential opioid-related overdose without a direct prescription. Opioid Overdose Education and Naloxone programs include law enforcement agencies, drug treatment programs, local health departments,

hospitals, urgent care facilities, or other community-based organizations that do not have access to a standing order through their organization.

LIMITATIONS ON DAYS' SUPPLY

Rx limited to 30 day supply

AVAILABILITY OF TREATMENT RESOURCES: The state Department of Human Services lists treatment services here: https://www.dhs.state.il.us/page.aspx?item=29725

INDIANA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescriber who is permitted to prescribe ephedrine, pseudoephedrine, or a controlled substance must be certified to receive information from the INSPECT program.

PDMP DELEGATE ACCESSIBILITY

Prescriber delegates are permitted if they are approved and supervised by a registered prescriber to make patient requests on behalf of the supervisor.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

2 hours on the topic of opioid prescribing and abuse are required.

NALOXONE AND SUBOXONE AVAILABILITY

The Indiana State Department of Health has distributed free naloxone kits to local health departments.

LIMITATIONS ON DAYS' SUPPLY

7 days for initial prescriptions.

AVAILABILITY OF TREATMENT RESOURCES: The Division of Mental Health and Addiction maintains information about treatment resources here: https://www.in.gov/fssa/addiction/

IOWA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescribing physician must check the PMP when issuing a prescription for an opioid.

PDMP DELEGATE ACCESSIBILITY

The number of designated agents/delegates is not limited in the PMP. Practitioners can authorize as many delegates as they wish, as long as those delegates are actively working with the practitioner.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

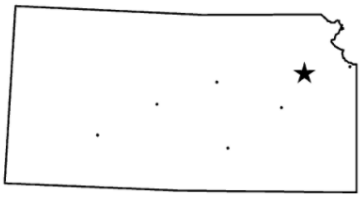
NALOXONE AND SUBOXONE AVAILABILITY

Iowa pharmacists may dispense naloxone by a standing order to an individual at risk of an opioid-related overdose or to a person who may be in a position to assist an individual at risk of an opioid-related overdose. The Medical Director and State Epidemiologist with the Iowa Department of Public Health, has authorized a statewide standing order that is available to all Iowa pharmacists who have met the required training criteria.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Iowa Department of Public Health maintains information regarding treatment resources here: https://idph.iowa.gov/substance-abuse/resources

KANSAS



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prescribers should check K-TRACS before prescribing controlled substances to ensure patient safety and avoid overlapping prescriptions or duplicating prescriptions from other prescribers.

PDMP DELEGATE ACCESSIBILITY

Each prescriber and pharmacist is allowed up to 10 delegates, but K-TRACS advises you should limit the number of delegates to ensure effective supervision. You should select staff such as licensed nurses or registered pharmacy technicians to act on your behalf in the K-TRACS system.
Delegates cannot use K-TRACS through an integrated system — only prescribers and pharmacists can — so it's important to encourage them to register and help them complete the registration process by adding them to the prescriber's account.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

The physician should consider co-prescribing naloxone when:

- prescribing an opioid, individually, or in aggregate with, other medications, greater than or equal to 50 MME/day;
- prescribing any dose of opioid when a benzodiazepine has been prescribed in the past 30 days or will be prescribed at the current visit; or
- prescribing any dose of an opioid to a patient with a prior history of opioid use disorder (OUD) or overdose, consider co-prescribing naloxone.

Additional reasons to consider co-prescribing naloxone are found here: https://pharmacy.ks.gov/k-tracs/prescribers/naloxone-co-prescribing

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: A list of Kanas based opioid treatment programs can be found here: https://www.kdads.ks.gov/docs/default-source/csp/opioid-str/opioid-treatment-programs-in-kansas.pdf?sfvrsn=1b8607ee_0

KENTUCKY

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Checking the PDMP is required when prescribing any schedule II controlled substance or a schedule III containing hydrocodone.

PDMP DELEGATE ACCESSIBILITY

KASPER Master Account Holders (MAHs) are permitted by statute to establish delegates to request eKASPER reports on their behalf. A delegate must be an employee of the practitioner's practice acting under the specific direction of the practitioner. There is no limit on the number of delegates, though it is important that they be trustworthy to only access the database appropriately. The Master Account Holder must register any delegates.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

For each 3-year cycle, at least 4.5 hours of approved hours related to the use of KASPER, pain management, or addiction disorders are required for prescribers or dispensers of controlled substances.

NALOXONE AND SUBOXONE AVAILABILITY

Information regarding locations where naloxone is available without a prescription can be found here: https://nextdistro.org/kentucky#naloxone-finder

LIMITATIONS ON DAYS' SUPPLY

3 days for initial prescriptions.

AVAILABILITY OF TREATMENT RESOURCES: Information regarding available addiction treatment resources can be found here: https://findhelpnowky.org/ky

LOUISIANA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescriber or delegate must review the PMP record prior to initially prescribing any opioid to a patient and at least every 90 days if the treatment is ongoing. This does not apply if the prescription is for no more than a single 7 day supply.

PDMP DELEGATE ACCESSIBILITY

Prescribers and dispensers can designate an individual to act as an agent for the purposes of submitting information to or obtaining data from the PMP.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

All licensees with a CDS license must complete a 1-time 3-hour course on drug diversion training, best controlled substance prescribing practices, and appropriate addiction treatment.

NALOXONE AND SUBOXONE AVAILABILITY

The state has issued a standing order that allows for participating pharmacists to dispense Naloxone or other opioid antagonists to laypeople including caregivers, family, and friends of an opioid user.

LIMITATIONS ON DAYS' SUPPLY

7 days for initial adult prescription or any prescription for a minor.

AVAILABILITY OF TREATMENT RESOURCES: The Department of Health maintains a directory of Medication assisted Treatment Clinics and Providers here:
https://ldh.la.gov/index.cfm/directory/category/35

MAINE

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The requirement to check the PDMP for initial prescriptions of an opioid or benzodiazepine does not apply in an emergency room setting.

PDMP DELEGATE ACCESSIBILITY

Staff members of a licensed hospital who are authorized by the chief medical officer of the hospital, insofar as the information relates to a patient receiving care in the hospital's emergency department or receiving inpatient services or surgical services from the hospital.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

All prescribers of controlled substances must complete 3 hours of CME on prescription of opioids every 2 years.

NALOXONE AND SUBOXONE AVAILABILITY

Naloxone nasal spray is available without a prescription at any Maine pharmacy.

LIMITATIONS ON DAYS' SUPPLY

Limit to 7 days and 100 Morphine Milligram Equivalents (MME) per day
May exceed 100MME/day for:

- Active cancer
- Palliative care
- End of life care
- Hospice Care
- Part of substance abuse treatment
- When directly administered in Emergency Room, Inpatient setting, long-term care or residential treatment facility

AVAILABILITY OF TREATMENT RESOURCES: Information about available resources can be found here: https://thealliancemaine.org/do-you-need-help/

MARYLAND

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prescribers must request and assess PDMP data:

- Before beginning a new course of treatment with an opioid or benzodiazepine
- When a course of treatment with an opioid or benzodiazepine extends beyond 90 days. In this case, prescribers must query again at least every 90 days thereafter before prescribing or dispensing the opioid or benzodiazepine.

PDMP DELEGATE ACCESSIBILITY

Delegates include a non-prescribing licensed healthcare practitioner (i.e., a registered nurse or a licensed alcohol and drug abuse counselor) OR a staff member, regardless of any license status, who is employed by or under contract with the same practice as the prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

One hour on opioid prescribing is required every 2 years.

NALOXONE AND SUBOXONE AVAILABILITY

Anyone can get Naloxone at a Maryland pharmacy without a prescription.

LIMITATIONS ON DAYS' SUPPLY

Lowest effective dose of an opioid; and a quantity that is no greater than the quantity needed for the expected duration of pain

AVAILABILITY OF TREATMENT RESOURCES: The Department of Health maintains information regarding available treatment resources here:
https://bha.health.maryland.gov/OVERDOSE_PREVENTION/Pages/Get-Help-Now-2.aspx

MASSACHUSETTS

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

State law requires that all Massachusetts prescribers query the state Prescription Monitoring Program (PMP) database prior to every prescription for a Schedule II or III narcotic medication or a benzodiazepine. This does not apply to emergency care where use of the PMP will likely result in patient harm or for patients under 96 months.

PDMP DELEGATE ACCESSIBILITY

MassPAT allows non-prescribers to access MassPAT on behalf of enrolled prescribers. During enrollment, delegates must select prescribers who have enrolled in MassPAT for whom they will be a delegate.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

If the physician prescribes controlled substances, 3 credits in opioid education and pain management are required.

NALOXONE AND SUBOXONE AVAILABILITY

The Department of Public Health (DPH) has issued a statewide standing order that allows retail pharmacies to dispense naloxone without a prescription.

LIMITATIONS ON DAYS' SUPPLY

- maximum 7 day supply on prescriptions for opioids when issued to an adult for the first time.
- maximum 7 day supply on all opioid prescriptions for minors.

May Exceed 7 day supply of an opioid to adult or minor patients if:

- in the prescriber's medical judgment, a greater supply is necessary.
- in such a case, the condition must be documented in the patient's medical record and the prescriber must indicate that a non-opioid alternative was not appropriate to address the medical condition.
- law does not apply to opioid medications that are designed for the treatment of substance abuse or opioid dependence.

May Exceed 7 day supply of an opioid to adult or minor patients if:

- in the prescriber's medical judgment, a greater supply is necessary.
- In such a case, the condition must be documented in the patient's medical record and the prescriber must indicate that a non-opioid alternative was not appropriate to address the medical condition.
- law does not apply to opioid medications that are designed for the treatment of substance abuse or opioid dependence.

AVAILABILITY OF TREATMENT RESOURCES: Information regarding treatment can be found here: https://helplinema.org/

MICHIGAN

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Before prescribing or dispensing to a patient a controlled substance in a quantity that exceeds a 3-day supply, a licensed prescriber shall obtain and review a MAPS report concerning that patient.

PDMP DELEGATE ACCESSIBILITY

a. If a user is registered as a prescriber delegate and requests a MAPS report on the prescriber's behalf for the prescriber to review, this will be in compliance with regulations. A prescriber delegate must select the prescriber for whom he/she are requesting a MAPS report.
b. It is important that the prescriber reviews the MAPS report prior to prescribing or dispensing a schedule 2-5 controlled substance that exceeds a 3- day supply.
c. For the purposes of using MAPS, a prescriber may have 10 active delegate users, while a delegate user may run MAPS reports on behalf of 30 active licensed users (prescribers).

CME REQUIREMENTS FOR OPIOID PRESCRIBING

A minimum of 3 hours in pain and symptom management are required.

NALOXONE AND SUBOXONE AVAILABILITY

In 2016, Michigan passed a Naloxone standing order law. This allows a pharmacist to dispense Naloxone without an individual prescription and without identifying a particular patient. With this, the "prescription" comes from the standing doctor's order from the State.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Department of Health and Human Services contains information about seeking treatment, including directories of various service providers, here: https://www.michigan.gov/mdhhs/0,5885,7-339-71550_2941_4871_4877---,00.html

MINNESOTA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The PDMP must be checked before issuing an initial prescription for a schedule II through IV opiate controlled substance. The requirement does not apply if due to a medical emergency it is not possible for the prescriber to review the data before issuing the prescription.

PDMP DELEGATE ACCESSIBILITY

A prescriber may delegate the task of accessing the data. The use of the system by a delegate must be audited on at least a quarterly basis to ensure compliance with appropriate use.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

All licensed health care professionals may directly or by standing order, prescribe, dispense, distribute, or administer naloxone to a person without being subject to civil liability or criminal prosecution. Pharmacists, in collaboration with a registered practitioner, may enter a written protocol to provide naloxone to persons at risk for, or know of someone at risk for, opioid overdose.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The state maintains information regarding substance use disorder treatment resources here: https://sud.fasttrackermn.org/

MISSISSIPPI

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The prescriber must check on all opioid prescriptions for acute and/or chronic noncancerous/non-terminal pain upon issuance and must utilize the MPMP upon initial contact with new patients and at least every 3 months thereafter for all controlled medications other than opioids.

PDMP DELEGATE ACCESSIBILITY

A physician or physician assistant may have anyone as a delegate. A nurse practitioner must have a registered nurse or a licensed practical nurse a delegate. A supervisor may have as many delegates as they are comfortable supervising in the appropriate use of MSPMP. A delegate may be a delegate for multiple prescribers/supervisors.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

For licensees with DEA certificates, 5 hours of CME must be related to prescribing medications with an emphasis on controlled substances.

NALOXONE AND SUBOXONE AVAILABILITY

Through a standing order issued by the Mississippi State Department of Health, pharmacists are now permitted to dispense by request the narcotic blocker naloxone. A prescription from a doctor or other medical practitioner is not required.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The state maintains information regarding addiction treatment resources here: http://www.dmh.ms.gov/wp-content/uploads/2018/12/Alcohol-and-Drug-Resource-Directory-December-2018.pdf

MISSOURI

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT: N/A

PDMP DELEGATE ACCESSIBILITY: N/A

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

Missouri law authorizes pharmacists to dispense Naloxone without a prescription under a statewide Standing Order issued by the Missouri Department of Health and Senior Services or by protocol with a licensed physician.

LIMITATIONS ON DAYS' SUPPLY

Schedule II prescriptions to a 30-day supply, except that the amount may be increased to a three-month supply if the prescriber describes on the prescription form or otherwise indicates the medical reason for requiring a larger supply.

AVAILABILITY OF TREATMENT RESOURCES: The Department of Mental Health maintains information about treatment services, including various directories, here: https://dmh.mo.gov/alcohol-drug/help

MONTANA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

PDMP access is suggested but not mandatory.

PDMP DELEGATE ACCESSIBILITY

A physician may designate an authorized agent to access the data.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

The Department of Public Health and Human Services standing order authorizes pharmacists who maintain a current active license practicing in a pharmacy located in Montana to initiate a prescription and dispense a naloxone opioid antagonist formulation listed in this standing order.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: Information about treatment resources can be found here: https://dphhs.mt.gov/opioid/gethelp

NEBRASKA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

PDMP usage is encouraged but not mandated.

PDMP DELEGATE ACCESSIBILITY

State law permits delegates to access the system. The delegates must be entered using the prescriber's account.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Physicians must complete at least 3 hours of CME every 2 years regarding prescribing opioids, with at least half an hour covering PDMP's.

NALOXONE AND SUBOXONE AVAILABILITY

A standing order issued by the medical director of the Department of Health and Human Services permits pharmacies to dispense naloxone without a prescription.

LIMITATIONS ON DAYS' SUPPLY

For minors, 7-day limit for acute pain.

AVAILABILITY OF TREATMENT RESOURCES: Information regarding treatment resources can be found here: http://dhhs.ne.gov/Pages/Adult-Behavioral-Health.aspx

NEVADA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A practitioner shall, before issuing an initial prescription for a controlled substance listed in schedule II, III or IV, or an opioid listed in schedule V, and at least once every 90 days thereafter for the duration of the course of treatment using the controlled substance, obtain a patient utilization report (patient report) regarding the patient from the PDMP.

PDMP DELEGATE ACCESSIBILITY

A delegate can be assigned to access the report. Delegates must register and have their own PMP account.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

For MD's, two hours must be in misuse and abuse of controlled substances, opioid prescribing, or addiction. D.O.'s are not subject to the same requirement, though 2 hours are required in one of the following: ethics, pain management or addiction care (the choice of these categories is also required for MD's.

NALOXONE AND SUBOXONE AVAILABILITY

The Department of Health and Human Services has launched an app to facilitate the distribution of naloxone kits to community-based organizations and EMS agencies.

LIMITATIONS ON DAYS' SUPPLY

14 day limit for initial prescription of Schedule II-IV for acute pain. Limit of 90 MME/day for opioid not previously issued to patient or not been issued more than 19 days prior.

AVAILABILITY OF TREATMENT RESOURCES: Information about treatment services can be found here: https://www.nevada211.org/addiction-services/

NEW HAMPSHIRE

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prescribers are required to query the PDMP prior to prescribing an opioid (schedule II through IV) when treating a patient for acute pain and for the initial visit and a minimum of two times during the year when treating a patient with chronic pain. There is an exception when "an emergency department is experiencing a higher than normal patient volume such that querying the program database would materially delay care."

PDMP DELEGATE ACCESSIBILITY

A delegate can access the database in the prescriber's behalf.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Three hours in pain management are required. The law is intended to provide access to anyone who may be in a position to help someone experiencing an opioid-related overdose. The Attorney General has indicated that the law allows for standing orders, which means that a licensed medical provider can have a prescription on file at any pharmacy that will allow pharmacists to dispense naloxone to ANYONE requesting it.

NALOXONE AND SUBOXONE AVAILABILITY

There is no requirement that there be a prescriber-patient relationship.

LIMITATIONS ON DAYS' SUPPLY

Restrict prescription to less than or equal to 7 days unless the medical condition is documented, and appropriate clinical rationale is included in the patient's medical record.

AVAILABILITY OF TREATMENT RESOURCES: The Alcohol and Drug Addiction Hotline can be accessed here: https://addictionresource.com/addiction-and-rehab-hotlines/new-hampshire-numbers/

NEW JERSEY

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A prescriber or the prescriber's delegate shall access prescription monitoring information for a new or current patient consistent with the following:

1. The first time the practitioner prescribes a Schedule II controlled dangerous substance or any opioid to a new or current patient for acute or chronic pain; and
2. The first time the practitioner prescribes a benzodiazepine drug that is a Schedule III or Schedule IV controlled dangerous substance; and
3. If the practitioner has a reasonable belief that the person may be seeking a controlled dangerous substance, in whole or in part, for any purpose other than the treatment of an existing medical condition, such as for purposes of misuse, abuse, or diversion, the first time the practitioner or other person prescribes a non-opioid drug other than a benzodiazepine drug that is a Schedule III or Schedule IV controlled dangerous substance; and
4. Any time the practitioner prescribes a Schedule II controlled dangerous substance for acute or chronic pain to a patient receiving care or treatment in the emergency department of a general hospital;
5. On a quarterly basis (every three months) during the period of time a current patient continues to receive a prescription for a Schedule II controlled dangerous substance or for an opioid drug for acute or chronic pain, or for a benzodiazepine that is a Schedule III or Schedule IV controlled dangerous substance.

PDMP DELEGATE ACCESSIBILITY

Delegates are required to be licensed in the State of New Jersey as a registered nurse, licensed practical nurse, advanced practice nurse without prescriptive authority, physician assistant without prescriptive authority, athletic trainer who is employed at a clinical practice setting, dental hygienist, or registered dental assistant. Medical and dental residents authorized by a faculty member from a medical or dental teaching facility may also be delegates.
Certified medical assistants (CMA) and medical scribes who meet requirements set forth at may register as an unlicensed delegate. In order to register as an unlicensed delegate, CMAs must meet all requirements, certify that they have completed the necessary training and provide a copy of the certificate of completion from a State-approved program. In order to register as an unlicensed delegate, CMAs must

meet all requirements and certify that they have completed the necessary training and provide a copy of the certificate of completion from a State-approved program.
Before delegates are able to access NJPMP data, they must register and be linked to a prescriber who is registered with the NJPMP. The prescriber will be responsible for supervising his or her delegate's activities.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

One of the required Category 1 credits must be in topics concerning prescription opioids, including responsible prescribing, alternatives to opioids for managing and treating pain, and the risks and signs of abuse, addiction, and diversion.

NALOXONE AND SUBOXONE AVAILABILITY

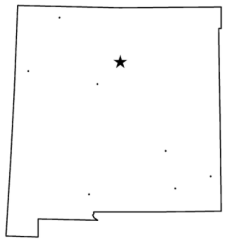
State law allows physicians to prescribe Naloxone to anyone in a position to assist others during an overdose (e.g., bystanders). The Department of Health will issue a standing order to any licensed pharmacist in good standing with the New Jersey Board of Pharmacy to dispense naloxone.

LIMITATIONS ON DAYS' SUPPLY

Prescription limited to 5 day supply for treatment of acute pain

AVAILABILITY OF TREATMENT RESOURCES: The state has information available about treatment here:
https://www.state.nj.us/humanservices/dmhas/resources/services/treatment/sa_other_resources.html

NEW MEXICO



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prescribers must check the PDMP before initially prescribing an opioid and quarterly thereafter.

PDMP DELEGATE ACCESSIBILITY

Delegates register with the PDMP and associates their profile with the account of the supervising prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

For MD's only (not DO's), if holding a DEA registration and license to prescribe opioids, 5 hours of related CME are required.

NALOXONE AND SUBOXONE AVAILABILITY

Physicians prescribing an opioid must co-prescribe an opioid antagonist to the patient if the prescription is for at least a 5-day supply.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Department of Health maintains information regarding treatment providers and programs here: https://www.nmhealth.org/about/ofm/ltcf/tlh/#resources

NEW YORK

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The general requirement to consult the PMP before prescribing a schedule II, III, or IV controlled substance does not apply to a 5-day supply prescribed from an emergency department of a general hospital.

PDMP DELEGATE ACCESSIBILITY

Practitioners can designate staff to look up patients on the PMP registry on their behalf. The designee, if unlicensed, will need to work with the HCS coordinator from their facility, or prescribing practitioner, to establish their own HCS account. After the designee obtains an HCS account user ID, the practitioner will need to log into the HCS, open the PMP application, and click on the Designation tab. On the designation screen, the practitioner will enter the HCS user ID of the individual that will be performing the look up on their behalf as a designee.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Prescribers with a DEA registration and residents prescribing controlled substances under a facility DEA registration must complete 3 hours of course work or training in pain management, palliative care, and addiction.

NALOXONE AND SUBOXONE AVAILABILITY

Naloxone is now available in more than 2,600 pharmacies throughout New York State. Individuals who are themselves at risk for an overdose or their family members or friends may acquire naloxone in these pharmacies without bringing in a prescription.

LIMITATIONS ON DAYS' SUPPLY

- Limit prescription to 7 day supply
- May Exceed 7 day supply:
    - chronic pain
    - cancer care
    - hospice

- end-of-life
- palliative care

AVAILABILITY OF TREATMENT RESOURCES: Information regarding various treatment options is maintained by the state here: https://oasas.ny.gov/treatment

NORTH CAROLINA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

N/A

PDMP DELEGATE ACCESSIBILITY

Delegates must register using the CSRS website.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Every physician prescribing controlled substances must complete at least 3 hours of Category 1 CME that includes instruction on controlled substance prescribing practices, recognizing signs of abuse or misuse, and prescribing for chronic pain management.

NALOXONE AND SUBOXONE AVAILABILITY

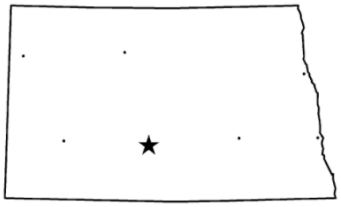
A delegate is authorized to obtain patient prescription histories on behalf of a designated prescriber or prescribers. Any individual who does not have prescriptive authority, such as an RN or administrative staff person, may register as a delegate.

LIMITATIONS ON DAYS' SUPPLY

5 days for initial prescription of Schedule II and III for acute pain.

AVAILABILITY OF TREATMENT RESOURCES: Information regarding regional resources can be found here: https://www.ncdhhs.gov/providers/lme-mco-directory

NORTH DAKOTA



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

If a physician prescribing any drug reported by the Prescription Drug Monitoring Program has reason to believe that a patient may be abusing or diverting prescribed medications, the physician shall access the Prescription Drug Monitoring Program and document the assessment of the monitoring results to help determine the proper treatment of the patient.

When a physician expects to prescribe reported drugs to a patient for a chronic condition or for a protracted basis, the physician shall request a PDMP report.

PDMP DELEGATE ACCESSIBILITY

A prescriber can delegate the authority to an individual that works for them or works for the same employer if the individual obtains their own "delegate account" by the same process the prescriber would use to gain access. The "supervisor/Practitioner" must create their account before a delegate can create and link the two accounts together. Eligible practitioner delegates would be a Registered Nurse, Licensed Practical Nurse, *or* Unlicensed Individual.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

North Dakota law allows anyone at risk for having or witnessing an opioid overdose to obtain a prescription. State law also permits many pharmacists to prescribe naloxone (see here: https://www.nodakpharmacy.com/naloxone/search.asp)

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The state maintains links to treatment resource information here: https://www.behavioralhealth.nd.gov/addiction/service-locator

OHIO

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The requirement to review an OARRS report when prescribing or dispensing an opioid does not apply when the reported drug is prescribed or furnished for a period not to exceed 7 days. However, this exemption shall not apply if the physician has reason to believe that the patient may be abusing or diverting reported drugs.

PDMP DELEGATE ACCESSIBILITY

Delegates need to be linked to each prescriber for whom they are requesting reports. A prescriber/supervisor may have as many delegates as they are comfortable supervising in the appropriate use of OARRS. A delegate may be a delegate for multiple prescribers/supervisors.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

A pharmacy may be authorized to dispense naloxone without a prescription in accordance with a physician-approved protocol.

The Pharmacy Board has also adopted a resolution to permit EMS agencies to receive or purchase naloxone from local law enforcement agencies that are not licensed by the Board of Pharmacy (this includes the replenishment of naloxone used at the scene of a suspected overdose). EMS agencies must maintain records of any naloxone purchase from or sale to local law enforcement (even if at no-cost).

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Department of Mental Health and Addiction Services maintains information regarding treatment services here: https://mha.ohio.gov/

OKLAHOMA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Physicians are required to check new patients or after 180 days elapsed since PMP check for the patient prior to prescribing one of the following: opiates, synthetic opiates, semi-synthetic opiates, benzodiazepine, or carisoprodol (exclusions for Hospice or end-of-life, or patients residing in nursing facility). This is applicable to the emergency department.

PDMP DELEGATE ACCESSIBILITY

Physicians may designate a staff member to run the patient PMP on the physician's behalf. This designated staff member must have their own PMP AWARxE account and have the physician listed as their supervisor.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

If holding a DEA registration number, each licensee must complete 1 hour of education in pain management or in opioid use or addiction in the yar preceding application for license renewal.

NALOXONE AND SUBOXONE AVAILABILITY

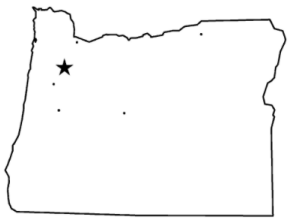
Naloxone is available without a prescription at many pharmacies throughout the state. A locator is available here: https://okimready.org/overdose/

The Department of Health reports that although first responders are permitted to carry and administer naloxone, few basic and intermediate level EMS and EMRAs have adopted the practice.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: Information regarding available resources can be found here: https://oklahoma.gov/odmhsas/substance-abuse/resources.html

OREGON



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

All prescribers are required to register with the system, but use is voluntary at this time.

PDMP DELEGATE ACCESSIBILITY

Authorized staff can access the system on behalf of prescribers.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

All licensees must complete a 1-hour pain management course, as well as 6 hours in pain management and/or the treatment of terminally ill patients.

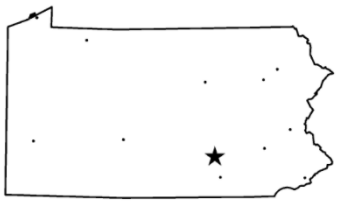
NALOXONE AND SUBOXONE AVAILABILITY

A pharmacist can prescribe, dispense, and distribute naloxone. Law that previously included special training requirements for recipients has been repealed.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: Information regarding Medication-Assisted Treatment, including a spreadsheet listing Oregon-Approved Opioid Treatment Programs, can be found here: https://www.oregon.gov/oha/HSD/AMH/Pages/MAT.aspx

PENNSYLVNIA



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Checking the PDMP is not required for any medication provided to a patient in the course of treatment while undergoing care in an emergency department. As part of good clinical practice, the Department of Health recommends that health care professionals check the system every time before a controlled substance(s) is prescribed or dispensed in any clinical setting.

PDMP DELEGATE ACCESSIBILITY

- Prescribers are authorized to grant Pennsylvania Prescription Drug Monitoring Program (PA PDMP) access to delegates under their employment for the purpose of querying the system on their behalf.
- A delegate is a person employed or supervised by a prescriber who granted them access to query the PA PDMP system on their behalf. Delegates are not required by law to be licensed healthcare professionals.
- Prescribers are responsible for ensuring the security of the PA PDMP system when used by a delegate. This includes ensuring that the delegates are using the PA PDMP appropriately, according to the acceptable use policy, and ensuring that delegate access is removed when an individual is no longer under their employ or supervision.
- A delegate must have their own account and password and it must not be shared with others.
- Prescribers must set explicit standards to qualify delegates authorized to query the system, which must (at minimum) meet the standards listed in the respective PA PDMP Acceptable Use Policy

CME REQUIREMENTS FOR OPIOID PRESCRIBING

2 hours of CME is required on pain management or identification of addiction, and an additional 2 hours on dispensing opioids.

NALOXONE AND SUBOXONE AVAILABILITY

The Secretary of Health has issued a standing order authorizing health care professionals to prescribe naloxone to eligible persons, including third party prescriptions.

LIMITATIONS ON DAYS' SUPPLY

- Limit Rx to 7 days, specifically applies to Urgent Cares, Emergency Providers or Observation Status in Hospital
- Limit Rx to 7 days for minors
- Must get written consent when prescribing opioids to minors
- May exceed 7 day supply when:
    - necessary for acute medical condition
    - when treating cancer pain or palliative care.
    - Rationale must be documented in chart

AVAILABILITY OF TREATMENT RESOURCES: The Pennsylvania Department of Drug and Alcohol Programs maintains a page designed to assist persons seeking treatment. It is here: https://apps.ddap.pa.gov/gethelpnow/CareProvider.aspx

RHODE ISLAND

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The Prescription Drug Monitoring Program (PDMP) shall be reviewed prior to starting any opioid.

PDMP DELEGATE ACCESSIBILITY

A prescriber is allowed to share access to the prescription drug monitoring database with an authorized designee of the practitioner, to consult the prescription drug monitoring database on the practitioner's and/or pharmacist's behalf. The designee must be employed by the same practice and in compliance with supervisory requirements of Rhode Island law for the PDMP. The actual user name and password that is used will be that of the prescriber and shared solely at the discretion of the professional.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

Prescribers are required to co-prescribe naloxone in these three different clinical scenarios. If co-prescribing naloxone is not appropriate for the patient, then the prescriber must document the reason(s) in the patient's medical record.

1. When prescribing an opioid individually or in aggregate with other medications that is more than or equal to 50 oral Morphine Milligram Equivalents (MMEs) per day.
2. When prescribing any dose of an opioid when a benzodiazepine has been prescribed in the past 30 days or will be prescribed at the current visit. Prescribers shall note in a patient's medical record the medical necessity of the co-prescription of the opioid and the benzodiazepine, and explain why the benefit outweighs the risk given the Food and Drug Administration (FDA) black box warning.
3. When prescribing any dose of an opioid to a patient with a prior history of opioid use disorder or overdose. Prescribers must also document in the patient's medical record the medical necessity of prescribing an opioid to this high-risk individual and explain why the benefit outweighs the risk given the patient's previous history.

Under a standing order, Naloxone is also available from any pharmacy.

LIMITATIONS ON DAYS' SUPPLY

- limit initial prescription for opioid in acute pain management on an outpatient basis to 30 morphine milligram equivalents (MME) total daily dose per day for a maximum total of 20 doses.
- Exceptions:
    - Cancer pain
    - nursing home patients
    - palliative care
    - Medications prescribed in the treatment of substance abuse or opioid dependence

AVAILABILITY OF TREATMENT RESOURCES

The Department of Behavioral Healthcare, Developmental Disabilities, and Hospitals' Bridgemark Physician Consult Program (**401-781-2700**) is designed to offer interested physicians immediate assistance with patients who may be at high risk for misuse of opioid medication. Physicians have several options for scheduling a patient assessment by a licensed Chemical Dependency Professional REFERRAL FORM, AUTHORIZATION AND DISCLOSURE FORM:

- A patient can be seen within one hour of the physician's referral while the patient is still at the provider's office. (A Bridgemark staff member will come to the physician's office.)
- A patient can be seen within one hour of the physician's referral at Bridgemark's office.
- A patient can be seen within three business days of the physician's referral at Bridgemark's office.
- A patient can be seen at his/her next office visit with the referring physician.

The results of the patient assessment will be discussed with the referring physician (as soon as possible after assessment and no later than seven business days after the assessment) and with the patient. Bridgemark is able to provide services to Spanish-speaking individuals and to anyone who is Deaf.

SOUTH CAROLINA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A practitioner, or the practitioner's authorized delegate, shall review a patient's controlled substance prescription history, as maintained in the prescription monitoring program, before the practitioner issues a prescription for a Schedule II controlled substance. This does not apply to a practitioner issuing a prescription for a Schedule II controlled substance that does not exceed a five-day supply for a patient.

PDMP DELEGATE ACCESSIBILITY

a) Practitioner must directly supervise the person(s) to whom access authority is delegated;
b) Practitioner, as holder of the master account for Prescription Monitoring Program (PMP) access, is responsible for delegate's use of the PMP;
c) The authorized delegate is responsible for any and all breaches of the Prescription Monitoring Act (PMA) and agrees to take responsibility for any violation of the Act;
d) Practitioner may delegate authority to access the PMP to no more than 3 delegate accounts;
e) Practitioner must re-confirm delegate account at least once every 180 days;
f) Practitioner as a master account holder, is responsible for deactivating delegate account upon delegate termination or when delegate access to the PMP is no longer needed.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

At least 2 hours of CME must be related to approved procedures for prescribing and monitoring schedules II-IV controlled substances.

NALOXONE AND SUBOXONE AVAILABILITY

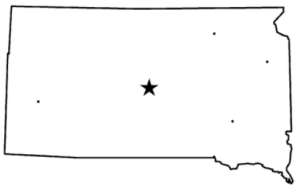
South Caroline law permits pharmacists to dispense Naloxone pursuant to a written joint protocol issued by the South Carolina Board of Medical Examiners and the South Carolina Board of Pharmacy without requiring a patient-specific written order or prescription.

LIMITATIONS ON DAYS' SUPPLY

Schedule II limited to 31 day supply

AVAILABILITY OF TREATMENT RESOURCES: The Department of Alcohol and Other Drug Abuse Services maintains directories of treatment options that can be accessed here: https://www.daodas.sc.gov/treatment/

SOUTH DAKOTA



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Use of the PDMP is encouraged but not required.

PDMP DELEGATE ACCESSIBILITY

Delegates must register in the system and be approved by the supervising prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING: N/A

NALOXONE AND SUBOXONE AVAILABILITY

Participating pharmacies may initiate a prescription and prescribe naloxone to an at risk person or third party connected to the same.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: A list of substance use disorder treatment agencies and services can be accessed here: https://dss.sd.gov/docs/behavioralhealth/community/Substance_Use_Disorder_Treatment_Agencies_and_Services.pdf

TENNESSEE

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

All healthcare practitioners are also required to check before dispensing an opioid or benzodiazepine as a new episode of treatment to a human patient the first time at that practice site and every six (6) months thereafter when said controlled substance remains a part of the treatment for that human patient after the initial dispensing.

This does not apply for prescriptions that do not exceed a single 3-day period with no refills.

PDMP DELEGATE ACCESSIBILITY

A delegate must register as a PDMP user and provide information necessary to be connected to the supervising prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

For D.O's, at least 2 hours must be designated specifically to address prescribing practices. For MD's, at least 2 hours must be given to controlled substance prescribing, which must include instruction in Medical Board treatment guidelines on opioids, benzodiazepines, barbiturates, and carisoprodol and may include topics such as addiction, risk management tools, and other topics approved by the Board.

NALOXONE AND SUBOXONE AVAILABILITY

The state maintains a list of anti-drug coalitions across the state that have access to naloxone. The list can be found here: https://www.tn.gov/opioids/treatment/preventing-an-overdose-death/find-naloxone-in-your-area.html

LIMITATIONS ON DAYS' SUPPLY

Pharmacies may dispense no more than a 30-day supply of schedule II substances. No restriction on the amount prescribed.

AVAILABILITY OF TREATMENT RESOURCES: Information regarding available services can be found here: https://www.tn.gov/behavioral-health/substance-abuse-services.html

TEXAS

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prescribers are required to check the patient's PMP history before dispensing or prescribing opioids, benzodiazepines, barbiturates, or carisoprodol. The reporting requirement applies to all Schedule II, III, IV, and V controlled substances.

The mandate does NOT apply to orders of controlled substances during an ER visit. It applies to discharge prescriptions.

PDMP DELEGATE ACCESSIBILITY

The Texas PMP allows prescribers to designate an unlimited number of delegates to access patient prescription data and generate reports on their behalf. Eligible prescriber delegates include nurses, medical residents, medical assistants, administrative staff, etc.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Licensees who practice direct patient care must complete at least 2 hours of CME regarding safe and effective pain management related to prescribing opioids and other controlled substances in each of the first 2 renewal periods following initial licensure and every 8 years thereafter.

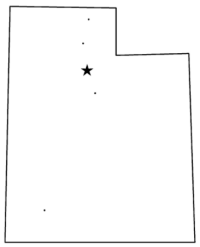
NALOXONE AND SUBOXONE AVAILABILITY

The standing order obtained by the state pharmacy association authorizes a pharmacist that is active and in good standing with the Texas State Board of Pharmacy and that has completed a required training to dispense an opioid antagonist.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: Information regarding local substance abuse services can be found here: https://hhs.texas.gov/services/mental-health-substance-use/mental-health-substance-use-resources/outreach-screening-assessment-referral

UTAH



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

a) A prescriber shall check the database for information about a patient before the first time the prescriber gives a prescription to a patient for a Schedule II opioid or a Schedule III opioid.
b) If a prescriber is repeatedly prescribing a Schedule II opioid or Schedule III opioid to a patient, the prescriber shall periodically review information about the patient.

This requirement may be waived if necessary due to an emergency situation.

PDMP DELEGATE ACCESSIBILITY
Licensed Practitioners with a Controlled Substance License may request proxy access to the CSD for properly trained designees. While there is no limit on the number of designees a practitioner may have, the practitioner is responsible for each designee, and any searches performed.

A person employed in an emergency department may access the database at the request of a licensed practitioner.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

A controlled substance prescriber must complete at least 3.5 hours in controlled substance prescribing.

NALOXONE AND SUBOXONE AVAILABILITY

Under a standing order from the Department of Health, a pharmacist may dispense naloxone to a person at risk of overdose or a family member, friend, or other person who could assist a person at increased risk.

LIMITATIONS ON DAYS' SUPPLY

- Schedule II and III opiates for acute pain may not exceed 7 days.
- Schedule II drugs cannot be prescribed greater than a 1 month supply

AVAILABILITY OF TREATMENT RESOURCES: The Department of Human Services maintains lists of treatment services at this site: https://dsamh.utah.gov/

VERMONT

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Before writing a prescription for a Schedule II, III or IV controlled substance, the prescriber must query the PDMP.

PDMP DELEGATE ACCESSIBILITY

Delegates are individuals employed by prescribers and are authorized to access the VPMS database related to the clinical care of bona fide current patients of the authorizing health care prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

For MD's, at least 2 hours must be on safe and effective prescribing of controlled substances and pain management.

NALOXONE AND SUBOXONE AVAILABILITY

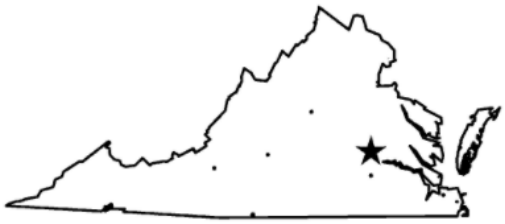
The Department of Health has issued a standing order that may be used by Eligible Persons as a prescription or third-party prescription to obtain Narcan. This order is authorization for pharmacists to dispense naloxone and devices for its administration in the forms prescribed herein.

LIMITATIONS ON DAYS' SUPPLY

- Mild pain: 24 MME/day
- Moderate pain: 32 MME/day
- Extreme pain: 50 MME/day

AVAILABILITY OF TREATMENT RESOURCES: The state maintains information about available treatment options here: https://www.healthvermont.gov/alcohol-drug-abuse/how-get-help/find-treatment

VIRGINIA



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

The Code of Virginia as it relates to the Virginia PMP requires a prescriber to query the PMP prior to prescribing (1) opioids for treatment exceeding seven days and prior to prescribing (2) medications (e.g., buprenorphine) for opioid use disorder.

PDMP DELEGATE ACCESSIBILITY

Prescribers may have as many delegates as they need, and delegates are no longer required to hold a license, registration or certificate from one of Virginia's health regulatory boards.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

2 hours must be in pain management, proper prescribing of controlled substances, and the diagnosis and management of addiction.

NALOXONE AND SUBOXONE AVAILABILITY

A standing order from the Department of Health authorizes licensed pharmacists and EMS personnel to dispense Naloxone.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: Information about treatment can be located here: https://findtreatment.gov/results

WASHINGTON

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Review of an EDIE report (or the lack of a report being generated because of no qualifying data) qualifies as compliance with checking the PMP.

PDMP DELEGATE ACCESSIBILITY

Providers may delegate mandatory PMP queries to an authorized healthcare designee, in line with the PMP requirements.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

A physician licensed to prescribe opioids must complete a one-time requirement of at least one hour regarding best practices in prescribing opioids or opioid prescribing rules in the administrative regulations.

NALOXONE AND SUBOXONE AVAILABILITY

People who want to get naloxone can use the standing order at any pharmacy in the state without a prescription from a health care provider.

LIMITATIONS ON DAYS' SUPPLY

A seven-day pill limit for acute prescriptions and 14 days for acute operative pain, with an exemption to these limits when clinical judgment is documented in the medical record.

AVAILABILITY OF TREATMENT RESOURCES: The Washington State Health Care Authority maintains information about substance abuse treatment resources here: https://www.hca.wa.gov/health-care-services-supports/behavioral-health-recovery/substance-use-treatment

WEST VIRGINIA

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Upon initially prescribing any Schedule II controlled substance, any opioid or any benzodiazepine to a patient who is not suffering from a terminal illness, and at least annually thereafter should the practitioner continue to treat the patient with a controlled substance, shall access the West Virginia Controlled Substances Monitoring Program Database for information regarding specific patients.

PDMP DELEGATE ACCESSIBILITY

You can serve as a delegate for a PDMP-registered Prescriber and must meet the definition of a Delegate by falling under one of the following two conditions:

a) a licensed healthcare professional such as a nurse, professional counselor, therapist, psychologist, social worker, certified pharmacy technician, pharmacist resident, etc.
b) employed by or under contract with the same professional practice as the registered Prescriber.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

Prior to renewal every physician must complete a minimum of 3 hours of drug diversion training and best practice prescribing of controlled substances. The training program must be approved by the Board.

NALOXONE AND SUBOXONE AVAILABILITY

The Department of Health and Human Resources has issued a standing order to be used by eligible persons as a prescription or third party prescription to obtain Naloxone from a pharmacy.

LIMITATIONS ON DAYS' SUPPLY

4-day supply of an opioid for outpatient use for an adult seeking care in an emergency department.

AVAILABILITY OF TREATMENT RESOURCES: The Bureau of Behavioral Health maintains information regarding treatment resources here: https://dhhr.wv.gov/BHHF/SECTIONS/PROGRAMS/PROGRAMSPARTNERSHIPS/ALCOHOLISMANDDRUGABUSE/Pages/default.aspx

WISCONSIN

PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

A practitioner, or a practitioner delegate assisting the practitioner in accordance with the standards of practice for the practitioner's profession, shall review the monitored prescription drug history report about a patient before the practitioner issues a prescription order for the patient. There is an exception if the prescription order is intended to last the patient for 3 days or less and is not subject to refill.

PDMP DELEGATE ACCESSIBILITY

Yes, delegates are permitted to access information on behalf of the healthcare professionals that supervise them.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

2 hours must be completed on the Medical Board’s opioid prescribing guidelines.

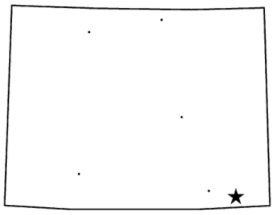
NALOXONE AND SUBOXONE AVAILABILITY

The Statewide Standing Order for Naloxone allows pharmacists in Wisconsin to sell naloxone without a health care provider's prescription to anyone at risk of an opioid overdose, as well as their family, friends, and anyone who may witness an opioid overdose.

LIMITATIONS ON DAYS’ SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: Information about substance use disorders and access to treatment is maintained by the state here: https://www.dhs.wisconsin.gov/aoda/sudindex.htm

WYOMING



PDMP MANDATES IMPACTING THE EMERGENCY DEPARTMENT

Prior to writing a prescription for a schedule II, III, IV, or V controlled substance, providers are required to search the state PMP database, as well as every 3 months thereafter for as long as the patient remains on a controlled substance. The provision only applies to schedule V if it is an opioid.

PDMP DELEGATE ACCESSIBILITY

Delegates must register with the system in order to access information for prescribers. A practitioner may appoint up to 2 delegates. A delegate registered with one practitioner may performs searches for others.

CME REQUIREMENTS FOR OPIOID PRESCRIBING

The board shall require three (3) hours of continuing education related to the responsible prescribing of controlled substances or treatment of substance abuse disorders every two (2) years.

NALOXONE AND SUBOXONE AVAILABILITY

Wyoming law allows pharmacists to prescribe naloxone to individuals. Anyone can go to a local pharmacy and ask about obtaining naloxone.

First responders may apply to receive grant funding for Narcan® Nasal Spray, currently the only FDA-approved intranasal naloxone. Agencies must obtain a standing order (a prescription from a provider for a group, not an individual) to purchase naloxone.

Other organizations can get Naloxone by applying through the Wyoming Department of Health. Agencies must obtain a standing order (a prescription from a provider for a group, not an individual) to purchase naloxone.

LIMITATIONS ON DAYS' SUPPLY: N/A

AVAILABILITY OF TREATMENT RESOURCES: The Wyoming Department of Health maintains information about treatment providers here: https://health.wyo.gov/behavioralhealth/mhsa/treatment/

Exhibit 9

FDA Grants PROP Petition (in Part), Proposes New Labeling and Requires Post-Marketing Studies for ER/LA Opioid Analgesics

September 16, 2013

By Delia A. Stubbs –

As previously reported, the Physicians for Responsible Opioid Prescribing ("PROP") filed a Citizen Petition in March requesting that FDA limit the labeling of "controlled release" opioids to severe-only pain in non-cancer patients. The petition also requested that FDA impose certain quantity and day limits on those medications.

After over 1900 comments on the petition were posted, including a rare endorsement by DEA, FDA issued its response last week ("PROP Petition Response"). (FDA also responded to another similar petition, here). Therein, FDA granted and rejected in part PROP's requests. FDA agreed to propose changes to the approved labeling of all Extended-Release/Long-Acting ("ER/LA") opioid analgesics, but rejected PROP's request for quantity and day limits. It also rejected PROP's request that the labeling changes be limited to "non-cancer" pain.

In sum, FDA's proposal, which it issued pursuant to its authority under Section 505(o) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), requests that all ER/LA opioid application holders, including NDA, BLA, and ANDA holders, modify those products' labels as follows:

- Change the indication to "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." This change deletes the reference to moderate pain and adds the requirement to rule out other treatment options. FDA explained that the change is intended to encourage prescribing decisions based on an individualized assessment. PROP Petition Response at 8.
- Add to the Limitations of Use section: "Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [the product] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain." Id.
- Change the boxed warning to include the risk of neonatal opioid withdrawal syndrome (NOWS) and to urge providers to asses and monitor the patient's risk of abuse/misuse of the drug.

FDA's full changes are captured in its letter to affected application holders ("FDA Letter").

FDA explained its reasoning for imposing these changes on ER/LA opioid analgesics only. FDA's decision is based on data demonstrating that the risk associated with these medications is greater than it is for their immediate-release counterparts. See PROP Petition Response at 7.

FDA rejected, however, PROP's requests to impose quantity and day limits on these medications. FDA stressed that it could not grant those requests based on the data submitted by PROP, noting, among other reasons, that "creating a maximum dose of 100 mg MED, or another dose ceiling, could imply a superior opioid safety profile under that set threshold, when there are no data to support such a conclusion." PROP Petition Response at 12.

Likewise, pursuant to its authority under Section 505(o), FDA is requiring ER/LA opioid analgesic application holders to conduct post-marketing studies to evaluate, among other things, the impact of long-term use of these medications on misuse, abuse, hyperalgesia, addiction, overdose, and death. Interestingly, the scope of the data requested by FDA extends beyond the mere physiological effects of these drugs to behavioral and social phenomena associated with their misuse and abuse. For example, FDA is requesting that holders conduct "a study to define and validate 'doctor/pharmacy shopping' as outcomes suggestive of misuse, abuse and/or addiction" that will then be used to inform the design and analysis of a study providing "quantitative estimates" of their "serious risks." See FDA Letter at 3-4. Currently, concerns regarding doctor/pharmacy shopping are addressed on a federal level through enforcement actions by DEA. FDA stated it expects application holders to "work together" to complete the post-approval studies. It set milestones for completion which range from 2014 to 2018.

So, what impact will these changes have on industry? From a law enforcement perspective, likely little-to-none. DEA's enforcement actions against physicians, pharmacists, and other registrants, are predicated on proof that controlled substances were prescribed for "illegitimate medical purposes," and that determination is based on an interpretation of state law, which permits physicians to prescribe drugs for "off-label" purposes. However, physician and pharmacy boards may more carefully scrutinize the prescribing and dispensing of medications for off-label purposes, and may consider the treatment recommendations provided in these products' labeling, if revised as FDA intends, as instructive of the standard of care.

The results of the post-marketing studies could also inform FDA's decision-making regarding scheduling recommendations for these and other drugs with potential risks of abuse. One potential outcome would be the obtainment of an acceptable measure of a substance's abuse potential, which is a required finding for determining whether, and in which category, to schedule a drug (or other substance) for control by DEA. In a recent advisory committee meeting regarding the up-scheduling of hydrocodone combination products, clear concerns arose regarding the lack of such an agreed upon standard. See our previous post, here.

Douglas Throckmorton, M.D., Deputy Director of Regulatory Programs in FDA's Center for Drug Evaluation and Research, stated "[t]he new labeling requirements and other actions are intended to help prescribers and patients make better decisions about who benefits from the use of these medications." Some might welcome these changes as a substitute for enforcement actions targeted at removing that discretion. See Larry Houck, AMA Tells Pharmacists: "Don't Call Us We'll Call You."

In response to FDA's action, all ER/LA opioid analgesic application holders must submit a prior-approval supplement with revised labeling consistent with FDA's proposal, or a declination and a

statement of reasons for the declination, by October 10, 2013. FDA stated that it may, after discussions with stakeholders, issue an order directing these (or other) labeling changes.

Exhibit 10

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

INTERIM UPDATE

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 193, MARCH 2018

(Replaces Practice Bulletin Number 191, February 2018)

Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the Committee on Practice Bulletins—Gynecology in collaboration with Kurt T. Barnhart, MD, MSCE; and Jason M. Franasiak, MD, TS (ABB).

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to clarify the guidance on the assessment of hCG levels after uterine aspiration in women with a pregnancy of unknown location.

Tubal Ectopic Pregnancy

Ectopic pregnancy *is defined as a pregnancy that occurs outside of the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube. Most cases of tubal ectopic pregnancy that are detected early can be treated successfully either with minimally invasive surgery or with medical management using methotrexate. However, tubal ectopic pregnancy in an unstable patient is a medical emergency that requires prompt surgical intervention. The purpose of this document is to review information on the current understanding of tubal ectopic pregnancy and to provide guidelines for timely diagnosis and management that are consistent with the best available scientific evidence.*

Background

Epidemiology

According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies (1). However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992 (1). Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality (2). The prevalence of ectopic pregnancy among women presenting to an emergency department with first-trimester vaginal bleeding, or abdominal pain, or both, has been reported to be as high as 18% (3).

Etiology

The fallopian tube is the most common location of ectopic implantation, accounting for more than 90% of cases (4). However, implantation in the abdomen (1%), cervix (1%), ovary (1–3%), and cesarean scar (1–3%) can occur and often results in greater morbidity because of delayed diagnosis and treatment (4). An ectopic pregnancy also can co-occur with an intrauterine pregnancy, a condition known as heterotopic pregnancy. The risk of heterotopic pregnancy among women with a naturally achieved pregnancy is estimated to range from 1 in 4,000 to 1 in 30,000, whereas the risk among women who have undergone in vitro fertilization is estimated to be as high as 1 in 100 (5, 6).

Risk Factors

One half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors (3). Women with a history of ectopic pregnancy are at increased risk of recurrence. The chance of a repeat ectopic pregnancy in a woman with a history of one ectopic pregnancy is approximately 10% (odds ratio [OR] 3.0; 95% CI, 2.1–4.4). In a woman with two or more prior ectopic pregnancies, the risk of recurrence increases to more than 25% (OR, 11.17; 95% CI, 4.0–29.5) (3). Other important risk factors for ectopic pregnancy include previous damage to the fallopian tubes, factors secondary to ascending pelvic infection, and prior pelvic or fallopian tube surgery (3, 7). Among women who become pregnant through the use of assisted reproductive technology, certain factors such as tubal factor infertility and multiple

embryo transfer are associated with an increased risk of ectopic pregnancy (8, 9). Women with a history of infertility also are at increased risk of ectopic pregnancy independent of how they become pregnant (7). Other less significant risk factors include a history of cigarette smoking and age older than 35 years (7).

Women who use an intrauterine device (IUD) have a lower risk of ectopic pregnancy than women who are not using any form of contraception because IUDs are highly effective at preventing pregnancy. However, up to 53% of pregnancies that occur with an IUD in place are ectopic (10). Factors such as oral contraceptive use, emergency contraception failure, previous elective pregnancy termination, pregnancy loss, and cesarean delivery have not been associated with an increased risk of ectopic pregnancy (3, 7, 11, 12).

Clinical Considerations and Recommendations

▶ ***How is an ectopic pregnancy diagnosed?***

The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.

Women with clinical signs and physical symptoms of a ruptured ectopic pregnancy, such as hemodynamic instability or an acute abdomen, should be evaluated and treated urgently. Early diagnosis is aided by a high index of suspicion. Every sexually active, reproductive-aged woman who presents with abdominal pain or vaginal bleeding should be screened for pregnancy, regardless of whether she is currently using contraception (13, 14). Women who become pregnant and have known significant risk factors should be evaluated for possible ectopic pregnancy even in the absence of symptoms.

Transvaginal Ultrasonography

Ultrasonography can definitively diagnose an ectopic pregnancy when a gestational sac with a yolk sac, or embryo, or both, is noted in the adnexa (15, 16); however, most ectopic pregnancies do not progress to this stage (15). The ultrasound findings of a mass or a mass with a hypoechoic area that is separate from the ovary should raise suspicion for the presence of an ectopic pregnancy; however, its positive predictive value is only 80% (15) because these findings can be confused with pelvic structures, such as a paratubal cyst, corpus luteum, hydrosalpinx, endometrioma, or bowel. Although an early intrauterine gestational sac may be visualized as early as 5 weeks of gestation (17), definitive ultrasound evidence of an intrauterine pregnancy includes visualization of a gestational sac with a yolk sac or embryo (16). Visualization of a definitive intrauterine pregnancy eliminates ectopic pregnancy except in the rare case of a heterotopic pregnancy. Although a hypoechoic "sac-like" structure (including a "double sac sign") (18) in the uterus likely represents an intrauterine gestation, it also may represent a pseudogestational sac, which is a collection of fluid or blood in the uterine cavity that is sometimes visualized with ultrasonography in women with an ectopic pregnancy (19, 20).

Serum Human Chorionic Gonadotropin Measurement

Measurement of the serum hCG level aids in the diagnosis of women at risk of ectopic pregnancy. However, serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient's history, symptoms, and ultrasound findings (21, 22). Accurate gestational age calculation, rather than an absolute hCG level, is the best determinant of when a normal pregnancy should be seen within the uterus with transvaginal ultrasonography (23, 24). An intrauterine gestational sac with a yolk sac should be visible between 5 weeks and 6 weeks of gestation regardless of whether there are one or multiple gestations (25, 26). In the absence of such definitive information, the serum hCG level can be used as a surrogate for gestational age to help interpret a nondiagnostic ultrasonogram.

The "discriminatory level" is the concept that there is a hCG value above which the landmarks of a normal intrauterine gestation should be visible on ultrasonography. The absence of a possible gestational sac on ultrasound examination in the presence of a hCG measurement above the discriminatory level strongly suggests a nonviable gestation (an early pregnancy loss or an ectopic pregnancy). In 50–70% of cases, these findings are consistent with an ectopic pregnancy (27–29). However, the utility of the hCG discriminatory level has been challenged (24) in light of a case series that noted ultrasonography confirmation of an intrauterine gestational sac on follow-up when no sac was noted on initial scan and the serum hCG level was above the discriminatory level (30–32). If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue (24, 32). Women with a multiple gestation have higher hCG levels than those with a single gestation at any given gestational age and may have hCG levels above traditional discriminatory hCG levels before ultrasonography recognition (24).

Trends of Serial Serum Human Chorionic Gonadotropin

A single hCG concentration measurement cannot diagnose viability or location of a gestation. Serial hCG concentration measurements are used to differentiate normal from abnormal pregnancies (21, 22, 33, 34). When clinical findings suggest an abnormal gestation, a second hCG value measurement is recommended 2 days after the initial measurement to assess for an increase or decrease. Subsequent assessments of hCG concentration should be obtained 2–7 days apart, depending on the pattern and the level of change.

In early pregnancy, serum hCG levels increase in a curvilinear fashion until a plateau at 100,000 mIU/mL by 10 weeks of gestation. Guidelines regarding the minimal increase in hCG for a potentially viable intrauterine pregnancy have become more conservative (ie, slower increase) (21, 22) and have been demonstrated to be dependent on the initial value (35). There is a slower than expected increase in serum hCG levels for a normal gestation when initial values are high. For example, the expected rate of increase is 49% for an initial hCG level of less than 1,500 mIU/mL, 40% for an initial hCG level of 1,500–3,000 mIU/mL, and 33% for an initial hCG level greater than 3,000 mIU/mL (35). In early pregnancy, an increase in serum hCG of less than a minimal threshold in 48 hours is suspicious of an abnormal pregnancy (ectopic or early pregnancy loss) because 99% of normal intrauterine pregnancies will have a rate of increase faster than this minimum. However, even hCG patterns consistent with a growing or resolving gestation do not eliminate the possibility of an ectopic pregnancy (36).

Decreasing hCG values suggest a failing pregnancy and may be used to monitor spontaneous resolution, but this decrease should not be considered diagnostic. Approximately 95% of women with a spontaneous early pregnancy loss will have a decrease in hCG concentration of 21–35% in 2 days depending on initial hCG levels (34). A woman with decreasing hCG values and a possible ectopic pregnancy should be monitored until nonpregnant levels are reached because rupture of an ectopic pregnancy can occur while levels are decreasing or are very low.

Pregnancy of Unknown Location

A pregnant woman without a definitive finding of an intrauterine or ectopic pregnancy on ultrasound examination has a "pregnancy of unknown location" (37). A pregnancy of unknown location should not be considered a diagnosis, rather it should be treated as a transient state and efforts should be made to establish a definitive diagnosis when possible (16). A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management (22, 37). Follow-up to confirm a diagnosis of ectopic pregnancy in a stable patient, especially at first clinical encounter, is recommended to eliminate misdiagnosis and to avoid unnecessary exposure to methotrexate, which can lead to interruption or teratogenicity of an ongoing intrauterine pregnancy (16, 38, 39). The first step is to assess for the possibility that the gestation is advancing.

When the possibility of a progressing intrauterine gestation has been reasonably excluded, uterine aspiration can help to distinguish early intrauterine pregnancy loss from ectopic pregnancy by identifying the presence or absence of intrauterine chorionic villi. Choosing the appropriate time and intervention should be done through shared decision making, incorporating the patient's values and preferences regarding maternal risk and the possibility of interrupting a progressing pregnancy. If chorionic villi are found, then failed intrauterine pregnancy is confirmed and no further evaluation is necessary. If chorionic villi are not confirmed, hCG levels should be monitored, with the first measurement taken 12–24 hours after aspiration. A plateau or increase in hCG postprocedure suggests that evacuation was incomplete or there is a nonvisualized ectopic pregnancy, and further treatment is warranted. Although the change at which hCG is considered to have plateaued is not precisely defined, it would be reasonable to consider levels to have plateaued if they have decreased by less than 10–15%. Large decreases in hCG levels are more consistent with failed intrauterine pregnancy than ectopic pregnancy. In two small series of women undergoing uterine aspiration for pregnancy of unknown location, nearly all women with a decrease in hCG levels of 50% or greater within 12–24 hours after aspiration had failed intrauterine pregnancies (29, 40). Patients with a decrease in hCG of 50% or greater can be monitored with serial hCG measurements, with further treatment reserved for those whose levels plateau or increase, or who develop symptoms of ectopic pregnancy. Management of patients with an hCG decrease of less than 50% should be individualized, as while failed intrauterine pregnancy is more frequent, ectopic pregnancy risk is appreciable. One study (29) noted 55.6% of patients with ectopic pregnancies had an hCG decrease of more than 10%, 23.5% had a decrease of more than 30%, and 7.1% had a decrease of more than 50%. In a series of patients who had an initial decrease of hCG levels between 15% and 50% 12–24 hours after office uterine aspiration for pregnancy

of unknown location who were monitored with serial hCG measurement, 3 of 46 patients had rising or plateauing hCG levels necessitating treatment for ectopic pregnancy (41). The other patients had resolving hCG levels, and were presumed to have failed intrauterine pregnancies. Patients with an hCG decline between 15% and 50% 12–24 hours after aspiration require at least close follow-up with serial hCG measurement, with consideration of treatment for ectopic pregnancy based on clinical factors such as plateau or increase in hCG, development of symptoms, or high clinical suspicion or strong risk factors for ectopic pregnancy (29, 40, 41).

There is debate among experts about the need to determine pregnancy location by uterine aspiration before providing methotrexate (42, 43). Proponents cite the importance of confirming the diagnosis to avoid unnecessary exposure to methotrexate and to help guide management of the current pregnancy and future pregnancies (37, 42). Arguments against the need for a definitive diagnosis include concern about the increased risk of tubal rupture because of delay in treatment while diagnosis is established and the increased health-care costs associated with additional tests and procedures (43). However, with close follow-up during this diagnostic phase, the risk of rupture is low. In one large series with serial hCG measurement of women with pregnancies of unknown location, the risk of rupture of an ectopic pregnancy during surveillance to confirm diagnosis was as low as 0.03 % among all women at risk and as low as 1.7% among all ectopic pregnancies diagnosed (22). In addition, presumptive treatment with methotrexate has not been found to confer a significant cost savings or to decrease the risk of complications (44). The choice of performing a uterine aspiration before treatment with methotrexate should be guided by a discussion with the patient regarding the benefits and risks, including the risk of teratogenicity in the case of an ongoing intrauterine pregnancy and exposure to methotrexate.

▶ *Who are candidates for medical management of ectopic pregnancy?*

Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration (45). These patients generally also are candidates for surgical management. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach. Women who choose methotrexate therapy should be counseled about the importance of follow-up surveillance.

Methotrexate

Methotrexate is a folate antagonist that binds to the catalytic site of dihydrofolate reductase, which interrupts the synthesis of purine nucleotides and the amino acids serine and methionine, thereby inhibiting DNA synthesis and repair and cell replication. Methotrexate affects actively proliferating tissues, such as bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue. Systemic methotrexate has been used to treat gestational trophoblastic disease since 1956 and was first used to treat ectopic pregnancy in 1982 (46). There are no recommended alternative medical treatment strategies for ectopic pregnancy beyond intramuscular methotrexate. Although oral methotrexate therapy for ectopic pregnancy has been studied, the outcomes data are sparse and indicate that benefits are limited (47).

Contraindications

Box 1 lists absolute and relative contraindications to methotrexate therapy (45). Before administering methotrexate, it is important to reasonably exclude the presence of an intrauterine pregnancy. In addition, methotrexate administration should be avoided in patients with clinically significant elevations in serum creatinine, liver transaminases, or bone marrow dysfunction indicated by significant anemia, leukopenia, or thrombocytopenia. Because methotrexate affects all rapidly dividing tissues within the body, including bone marrow, the gastrointestinal mucosa, and the respiratory epithelium, it should not be given to women with blood dyscrasias or active gastrointestinal or respiratory disease. However, asthma is not an exclusion to the use of methotrexate. Methotrexate is directly toxic to the hepatocytes and is cleared from the body by renal excretion; therefore, methotrexate typically is not used in women with liver or kidney disease.

Relative contraindications for the use of methotrexate (Box 1) do not serve as absolute cut-offs but rather as indicators of potentially reduced effectiveness in certain settings. For example, a high initial hCG level is considered a relative contraindication. Systematic review evidence shows a failure rate of 14.3% or higher with methotrexate when pretreatment hCG levels are higher than 5,000 mIU/mL compared with a 3.7% failure rate for hCG levels less than 5,000 mIU/mL (48). Of note, studies often have excluded patients from methotrexate treatment when hCG levels are greater than

Box 1. Contraindications to Methotrexate Therapy

Absolute Contraindications

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient
- Inability to participate in follow-up

Relative Contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial hCG concentration
- Ectopic pregnancy greater than 4 cm in size as imaged by transvaginal ultrasonography
- Refusal to accept blood transfusion

Modified from Medical treatment of ectopic pregnancy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. Fertil Steril 2013;100:638–44.

5,000 mIU/mL based on expert opinion that these levels are a relative contraindication to medical management. Other predictors of methotrexate treatment failure include the presence of an advanced or rapidly growing gestation (as evidenced by fetal cardiac activity) and a rapidly increasing hCG concentration (greater than 50% in 48 hours) (48–50).

▶ ***What methotrexate regimens are used in the management of ectopic pregnancy, and how do they compare in effectiveness and risk of adverse effects?***

There are three published protocols for the administration of methotrexate to treat ectopic pregnancy: 1) a single-dose protocol (51), 2) a two-dose protocol (52), and 3) a fixed multiple-dose protocol (53) (Box 2). The single-dose regimen is the simplest of the three regimens; however, an additional dose may be required to ensure resolution in up to one quarter of patients (54, 55). The two-dose regimen was first proposed in 2007 in an effort to combine the efficacy of the multiple-dose protocol with the favorable adverse effect profile of the single-dose regimen (55). The two-dose regimen adheres to the same hCG monitoring schedule as the single-dose regimen, but a second dose of methotrexate is administered on day 4 of treatment. The multiple-dose methotrexate regimen involves up to 8 days of treatment with alternating administration of methotrexate and folinic acid, which is given as a rescue dose to minimize the adverse effects of the methotrexate.

The overall treatment success of systemic methotrexate for ectopic pregnancy, defined as resolution of the ectopic pregnancy without the need for surgery, in observational studies ranges from approximately 70% to 95% (55). Resolution of an ectopic pregnancy may depend on the methotrexate treatment regimen used and the initial hCG level. However, there is no clear consensus in the literature regarding the optimal methotrexate regimen for the management of ectopic pregnancy. The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.

Single-Dose Versus Multiple-Dose

Observational studies that compared the single-dose and multiple-dose regimens have indicated that although the multiple-dose regimen is statistically more effective (92.7% versus 88.1%, respectively; P=.035) (single-dose

Box 2. Methotrexate Treatment Protocols

Single-dose regimen*

- Administer a single dose of methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Measure hCG level on posttreatment day 4 and day 7
  - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
  - If decrease is less than 15%, readminister methotrexate at a dose of 50 mg/m² intramuscularly and repeat hCG level
  - If hCG does not decrease after two doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Two-dose regimen†

- Administer methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Administer second dose of methotrexate at a dose of 50 mg/m² intramuscularly on day 4
- Measure hCG level on posttreatment day 4 and day 7
  - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
  - If decrease is less than 15%, readminister methotrexate 50 mg/m² intramuscularly on day 7 and check hCG levels on day 11
  - If hCG levels decrease 15% between day 7 and day 11, continue to monitor weekly until reaching nonpregnant levels
  - If the decrease is less than 15% between day 7 and day 11, readminister dose of methotrexate 50 mg/m² intramuscularly on day 11 and check hCG levels on day 14
  - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Fixed multiple-dose regimen‡

- Administer methotrexate 1 mg/kg intramuscularly on days 1, 3, 5, 7; alternate with folinic acid 0.1 mg/kg intramuscularly on days 2, 4, 6, 8
- Measure hCG levels on methotrexate dose days and continue until hCG has decreased by 15% from its previous measurement
  - If the decrease is greater than 15%, discontinue administration of methotrexate and measure hCG levels weekly until reaching nonpregnant levels (may ultimately need one, two, three, or four doses)
  - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Abbreviation: hCG, human chorionic gonadotropin.

*Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 1993;168:1759-62; discussion 1762–5.

†Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. Fertil Steril 2007;87:250–6.

‡Rodi IA, Sauer MV, Gorrill MJ, Bustillo M, Gunning JE, Marshall JR, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. Fertil Steril 1986;46:811–3.

failure OR, 1.71; 95% CI, 1.04–2.82), the single-dose regimen is associated with a decreased risk of adverse effects (OR, 0.44; 95% CI, 0.31–0.63) (55). However, a more recent systematic review of randomized controlled trials showed similar rates of successful resolution with the single-dose and multiple-dose regimens (relative risk [RR], 1.07; 95% CI, 0.99–1.17) and an increased risk of adverse effects with the multiple-dose protocol (RR, 1.64; 95% CI, 1.15–2.34) (56).

Single-Dose Versus Two-Dose

A systematic review and meta-analysis of three randomized controlled trials showed similar rates of successful resolution for the two-dose and single-dose protocols (RR, 1.09; 95% CI 0.98–1.20) and comparable risk of adverse effects (RR, 1.33; 95% CI, 0.92–1.94) (56). However, in two of the three trials included in the review, the two-dose regimen was associated with greater success among women with high initial hCG levels. In the first trial, there was a nonstatistically significant trend toward greater success for the two-dose regimen in the subgroup with an initial hCG level greater than 5,000 mIU/mL (80.0% versus 58.8%, P=.279) (RR, 0.74; 95% CI, 0.47–1.16) (57). The second trial reported a statistically significant higher success rate for the two-dose regimen versus the single-dose regimen in patients with initial serum hCG levels between 3,600 mIU/mL and 5,500 mIU/mL (88.9% versus 57.9%, P=.03) (OR 5.80; 95% CI, 1.29–26.2) (58).

▶ What surveillance is needed after methotrexate treatment?

After administration of methotrexate treatment, hCG levels should be serially monitored until a nonpregnancy level (based upon the reference laboratory assay) is reached (51). Close monitoring is required to ensure disappearance of trophoblastic activity and to eliminate the possibility of persistent ectopic pregnancy. During the first few days after treatment, the hCG level may increase to levels higher than the pretreatment level but then should progressively decrease to reach a nonpregnant level (51). Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention (51). Methotrexate treatment failure in patients who did not undergo pretreatment uterine aspiration should raise concern for the presence of an abnormal intrauterine gestation. In these patients, uterine aspiration should be considered before repeat methotrexate administration or surgical management, unless there is clear evidence of a tubal ectopic pregnancy. Ultrasound surveillance of resolution of an ectopic pregnancy is not routinely indicated because findings do not predict rupture or time to resolution (59, 60). Resolution of serum hCG levels after medical management is usually complete in 2–4 weeks but can take up to 8 weeks (55). The resolution of hCG levels is significantly faster in patients successfully treated with the two-dose methotrexate regimen compared with the single-dose regimen (25.7+13.6 versus 31.9+14.1 days; P>.025) (57).

▶ What are the potential adverse effects of systemic methotrexate administration?

Adverse effects of methotrexate usually are dependent on dose and treatment duration. Because methotrexate affects rapidly dividing tissues, gastrointestinal problems (eg, nausea, vomiting, and stomatitis) are the most common adverse effects after multiple doses. Vaginal spotting is expected. It is not unusual for women treated with methotrexate to experience abdominal pain 2–3 days after administration, presumably from the cytotoxic effect of the drug on the trophoblastic tissue. In the absence of signs and symptoms of overt tubal rupture and significant hemoperitoneum, abdominal pain usually can be managed expectantly by monitoring a woman's hemoglobin level and intraperitoneal fluid amount with transvaginal ultrasonography.

Elevation of liver enzymes is a less commonly reported adverse effect and typically resolves after discontinuing methotrexate use (61). Alopecia also is a rare adverse effect of the low doses used to treat ectopic pregnancy. Cases of pneumonitis also have been reported, and women should be counseled to report any fever or respiratory symptoms to their physicians (62).

▶ How should women be counseled regarding the treatment effects of methotrexate?

Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed. It is important to educate patients about the symptoms of tubal rupture and to emphasize the need to seek immediate medical attention if these symptoms occur. Vigorous activity and sexual intercourse should be avoided until confirmation of resolution because of the theoretical risk of inducing rupture of the ectopic pregnancy. Additionally, practitioners should limit pelvic and ultrasound examinations when possible. Patients should be advised to avoid folic acid supplements, foods

that contain folic acid, and nonsteroidal antiinflammatory drugs during therapy because these products may decrease the efficacy of methotrexate. Avoidance of narcotic analgesic medications, alcohol, and gas-producing foods are recommended so as not to mask, or be confused with, escalation of symptoms of rupture. Sunlight exposure also should be avoided during treatment to limit the risk of methotrexate dermatitis (63).

Before treatment with methotrexate, women should be counseled about the potential for fetal death or teratogenic effects when administered during pregnancy. The product labeling approved by the U.S. Food and Drug Administration recommends that women avoid pregnancy during treatment and for at least one ovulatory cycle after methotrexate therapy (63). Methotrexate is cleared from the serum before the 4–12 weeks necessary for the resolution of the ectopic gestation and ovulation in the next cycle (64, 65). However, there are reports of methotrexate detectable in liver cells 116 days past exposure (66). Limited evidence suggests that the frequency of congenital anomalies or early pregnancy loss is not elevated in women who have become pregnant shortly after methotrexate exposure (66). However, perhaps based on the timing of methotrexate's clearance from the body, some experts continue to recommend that women delay pregnancy for at least 3 months after the last dose of methotrexate (67).

▶ *How does methotrexate treatment affect subsequent fertility?*

Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve. A prospective observational study noted no difference in anti-müllerian hormone levels or reproductive outcomes after administration of methotrexate (68). Furthermore, a systematic review of women undergoing fertility treatment found no significant differences in the mean number of oocytes retrieved during the cycles before and after methotrexate administration (69).

▶ *Who are candidates for surgical management of ectopic pregnancy?*

In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach. Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

Surgical management is necessary when a patient meets any of the absolute contraindications to medical management listed in Box 1 and should be considered when a patient meets any of the relative contraindications. Surgical management should be employed when a patient who initially elects medical management experiences a failure of medical management. Surgical treatment also can be considered for a clinically stable patient with a nonruptured ectopic pregnancy or when there is an indication for a concurrent surgical procedure, such as tubal sterilization or removal of hydrosalpinx when a patient is planning to undergo subsequent in vitro fertilization.

Surgical management generally is performed using laparoscopic salpingectomy (removal of part or all of the affected fallopian tube) or laparoscopic salpingostomy (removal of the ectopic pregnancy while leaving the affected fallopian tube in situ). Laparotomy typically is reserved for unstable patients, patients with a large amount of intraperitoneal bleeding, and patients in whom visualization has been compromised at laparoscopy.

▶ *How do medical management and surgical management of ectopic pregnancy compare in effectiveness and risk of complications?*

Medical management of ectopic pregnancy avoids the inherent risks of surgery and anesthesia. However, compared with laparoscopic salpingectomy, medical management of ectopic pregnancy has a lower success rate and requires longer surveillance, more office visits, and phlebotomy. Randomized trials that compared medical management of ectopic pregnancy with methotrexate to laparoscopic salpingostomy have demonstrated a statistically significant lower success rate with the use of single-dose methotrexate (relative rate for success, 0.82; 95% CI, 0.72–0.94) and no difference with the use of multidose methotrexate (relative rate for success, 1.8; 95% CI, 0.73–4.6) (70). Comparing systemic methotrexate with tube-sparing laparoscopic surgery, randomized trials have shown no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies (70).

Medical management of ectopic pregnancy is cost effective when laparoscopy is not needed to make the diagnosis and hCG values are less 1,500 mIU/mL (71). Surgical management of ectopic pregnancy is more cost

effective if time to resolution is expected to be prolonged, or there is a relatively high chance of medical management failure, such as in cases with high or increasing hCG values or when embryonic cardiac activity is detected (72, 73).

▶ *How do salpingostomy and salpingectomy compare in effectiveness and fertility outcomes in the management of ectopic pregnancy?*

The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage. Randomized controlled trials that compared salpingectomy with salpingostomy for the management of ectopic pregnancy have found no statistically significant difference in the rates of subsequent intrauterine pregnancy (RR, 1.04; 95% CI, 0.899–1.21) or repeat ectopic pregnancy (RR, 1.30; 95% CI, 0.72–2.38) (74). In contrast, cohort study findings indicate that salpingostomy is associated with a higher rate of subsequent intrauterine pregnancy (RR, 1.24; 95% CI, 1.08–1.42) but also with an increased risk of repeat ectopic pregnancy (10% versus 4%; RR, 2.27; 95% CI, 1.12–4.58) compared with salpingectomy (74).

In general, salpingectomy is the preferred approach when severe fallopian tube damage is noted and in cases in which there is significant bleeding from the proposed surgical site. Salpingectomy can be considered in cases of desired future fertility when the patient has a healthy contralateral fallopian tube. However, salpingostomy should be considered in patients who desire future fertility but have damage to the contralateral fallopian tube and in whom removal would require assisted reproduction for future childbearing. When salpingostomy is performed, it is important to monitor the patient with serial hCG measurement to ensure resolution of ectopic trophoblastic tissue. If there is concern for incomplete resection, a single prophylactic dose of methotrexate may be considered (45).

▶ *Who are candidates for expectant management of diagnosed ectopic pregnancy?*

There may be a role for expectant management of ectopic pregnancy in specific circumstances. Candidates for successful expectant management of ectopic pregnancy should be asymptomatic; should have objective evidence of resolution (generally, manifested by a plateau or decrease in hCG levels); and must be counseled and willing to accept the potential risks, which include tubal rupture, hemorrhage, and emergency surgery. If the initial hCG level is less than 200 mIU/mL, 88% of patients will experience spontaneous resolution; lower spontaneous resolution rates can be anticipated with higher hCG levels (75). In a single small randomized trial of women with hCG levels less than 2,000 mIU/mL, expectant management was not associated with a statistically significant lower treatment success than single-dose methotrexate for the management of ectopic pregnancy (59% versus 76%, respectively) (RR, 1.3; 95% CI, 0.9–1.8) (76). Reasons for abandoning expectant management include intractable or significantly increased pain, insufficient decrease of hCG levels, or tubal rupture with hemoperitoneum.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach.
- Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient's history, symptoms, and ultrasound findings.
- If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue.
- The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy

should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage.

- The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.
- Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention.
- Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve.
- There may be a role for expectant management of ectopic pregnancy in specific circumstances.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.
- A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management.
- Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration.
- After administration of methotrexate treatment, hCG levels should be serially monitored until a nonpregnancy level (based upon the reference laboratory assay) is reached.
- Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed.

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Tubal ectopic pregnancy. ACOG Practice Bulletin No. 193. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018; 131:e91–103.

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and September 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.
II-1 Evidence obtained from well-designed controlled trials without randomization.
II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

Exhibit 11

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

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

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

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

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

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

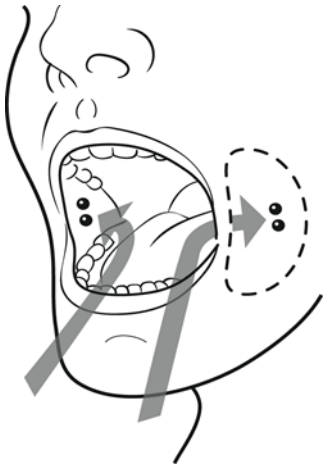
Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

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

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

    Figure 1

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

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

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

2.2 Patient Management Following Misoprostol Administration

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

Give the patient:

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

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)

- 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.

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.

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.

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

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

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.

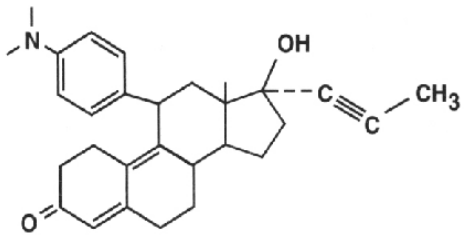
10 OVERDOSAGE

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

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.

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

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].

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.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

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

01/2023

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.

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.

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.

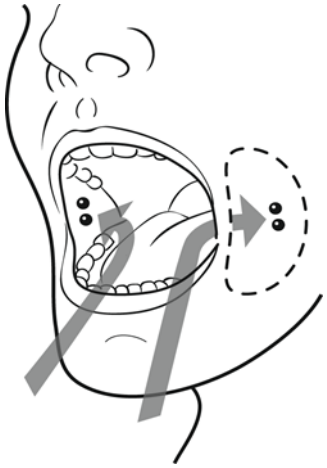


Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

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.

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 01/2023