RCM # 2007-525
NDA 20-687
Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2017

The following information is from United States post-marketing reports received by FDA of adverse events that occurred among patients who had taken mifepristone for medical termination of pregnancy. Because FDA has eliminated duplicate reports, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details, the numbers provided here may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. These events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use, and other possible medical or surgical treatments and conditions. The estimated number of women who have used mifepristone in the U.S. for the medical termination of pregnancy through the end of December 2017 is approximately 3.4 million women, an increase of approximately 163,000 since June 2017.

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

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

Date range of cumulative reports	09/28/00[†] - 12/31/17
Died [‡]	22
*Ectopic pregnancies [||]	97

[†] U.S. approval date

[‡] The fatal cases are included regardless of causal attribution to mifepristone. Deaths were associated with sepsis in eight of the 22 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and one case tested positive for *Clostridium perfringens*). Seven of the eight fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Thirteen of the fourteen remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; drug intoxication; suspected homicide; suicide; delayed onset toxic shock-like syndrome; hemorrhage; unintentional overdose resulting in liver failure; drug overdose of undetermined intent and cardiac arrest; combined drug intoxication/overdose; and a case of natural death due to severe pulmonary emphysema. In the fourteenth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. There were 11 additional reported deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure;" thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium septicum* sepsis (from a published literature report).

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

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

Table 2. Post-Marketing Adverse Events in U.S. Women Who Used Mifepristone for Medical Termination of Pregnancy

Date ranges of reports received	09/28/00[†] - 10/31/12	11/01/12 - 12/31/17[‡]
Cases with any adverse event	2740	1445
Hospitalized, excluding deaths	768	273
*Experienced blood loss requiring transfusions [§]	416	182
Infections [||] (*Severe infections [¶])	308 (57)	103 (12)

[†] U.S. approval date

[‡] FDA implemented the FDA Adverse Event Reporting System (FAERS) on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 2.

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

[§] As stated in the approved Mifeprex (mifepristone) labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

[||] This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.

[¶] This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.