

MIFEPREX® (MIFEPRISTONE)

Policy Number: 2018D0012N

Effective Date: June 1, 2018

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Related Policies
None

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Although Mifeprex (mifepristone) is an orally administered drug product, the Risk Evaluation and Mitigation Strategy associated with its use requires administration in the physician’s office clinic, or hospital.

The US Food and Drug Administration has granted approval of another mifepristone product, Korlym®, for the treatment of endogenous Cushing’s syndrome.²⁴ Notification criteria for Korlym are administered under the pharmacy benefit.

The member specific Certificate of Coverage must be referenced as some COCs contain explicit exclusions for abortion and related services. Mifepristone is a covered health service in Certificates of Coverage that do not explicitly exclude coverage for abortion and related services. Although most Certificates of Coverage explicitly exclude oral drugs administered in a physician office for non-emergency purposes, that exclusion does not apply to mifepristone.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Mifeprex (mifepristone), in combination with misoprostol, is proven and medically necessary for termination of pregnancy through 70 days gestation when administered under the supervision of a qualified physician.³ For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle.³

Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.^{3,25}

Mifeprex is unproven and not medically necessary for treatment of:

- Leiomyomata
- Endometriosis
- Breast cancer
- Ovarian cancer
- Meningioma
- Psychotic major depression
- Oral contraception
- Induction of labor

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Although Mifeprex is an orally administered drug product, the Risk Evaluation and Mitigation Strategy associated with its use requires administration in the physician's office.

Mifeprex, in combination with misoprostol, is indicated for the medical termination of intrauterine pregnancy through 70 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected. Patients taking Mifeprex must take 800 mcg, buccally, of misoprostol within 24 to 48 hours after taking Mifeprex unless a complete abortion has already been confirmed before that time. Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy.³

Prior to a physician using mifepristone in his/her practice, the physician must sign and return to Danco Laboratories the Prescriber's Agreement, indicating that they meet the qualifications and will observe the guidelines outlined below.²⁵ Danco Laboratories will not ship Mifeprex until they have the signed Prescriber Agreement on file. Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to the letter, and is also available by calling 1-877-4 Early Option (1-877-432-7596) or website: www.earlyoptionpill.com.

In addition to these qualifications, the physician must provide Mifeprex in a manner consistent with the following guidelines:²⁵

- Under federal law, each patient must be provided with a Medication Guide. The physician must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss them, obtain her signature on the Patient Agreement and sign it themselves.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. The physician must notify Danco Laboratories in writing as discussed in the Package Insert under the heading Dosage and Administration in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, the physician must report any hospitalization, blood transfusion, or other serious event to Danco Laboratories by providing a brief clinical and administrative synopsis of any such adverse events, and identifying the patient solely by package serial number to ensure patient confidentiality.
- The prescriber must follow additional specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters.

The FDA has published post-market drug safety information for patients and providers regarding Mifeprex and the risk for sepsis associated with its use.¹² Physicians and their patients should fully discuss early potential signs and symptoms that may warrant immediate medical evaluation. All providers of medical abortion and emergency room health care providers should investigate the possibility of sepsis in patients who are undergoing medical abortion and present with nausea, vomiting, or diarrhea and weakness with or without abdominal pain, and without fever or other signs of infection more than 24 hours after taking misoprostol. The FDA recommends that physicians suspect infection in patients with this presentation and consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as *Clostridium sordellii*.

Another mifepristone product, Korlym[®], is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.²⁴

BACKGROUND

Mifeprex (mifepristone) is a synthetic steroid with antiprogesterone effects. The anti-progesterone 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.³

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
S0190	Mifepristone, oral, 200 mg
S0191	Misoprostol, oral, 200 mcg

CLINICAL EVIDENCE

Proven

Medical Termination of Intrauterine Pregnancy Through 70 Days' Pregnancy

Mifeprex, in combination with misoprostol, is indicated for the medical termination of intrauterine pregnancy through 70 days' pregnancy.³

Unproven

Mifepristone has also been used in the treatment of endometriosis, breast and ovarian cancer, meningioma, induction of labor, and psychotic major depression.^{4-6, 11, 13-19} In addition, modest efficacy has been shown for the use of mifepristone in treatment of symptomatic leiomyomata.^{10,21-22} To date, the studies published on these diseases have

been small and most have been open-label trials. The use of mifepristone for any of these indications is considered unproven at this time. Mifepristone has also been studied as an estrogen-free oral contraceptive in small trials.^{9,20,23} Further study will need to be undertaken before mifepristone can be considered proven as an oral contraceptive.

Technology Assessment

In 2011, a Cochrane Database review was published which compared different medical methods for first trimester abortion. Authors' concluded that there are safe and effective medical abortion methods available.⁷

- Combined regimens (mifepristone & misoprostol) are more effective than single agents. In the combined regimen, the dose of mifepristone can be lowered to 200 mg without significantly decreasing the method effectiveness.
- Vaginal misoprostol is more effective than oral administration, and has less side effects than sublingual or buccal.

Professional Societies

World Health Organization, Department of Reproductive Health and Research

In 2012, the World Health Organization (WHO) updated its 2003 publication 'Safe abortion: technical and policy guidance for health systems.' Recommended methods for medical abortion between 63 and 84 days gestational age are as follows:⁸

- The recommended method for medical abortion is mifepristone followed by misoprostol.
- For pregnancies of gestational age between 9 and 12 weeks (63 and 84 days), the recommended method for medical abortion is mifepristone followed 36 to 48 hours later by misoprostol. (Strength of recommendation: weak.; quality of evidence based on one randomized controlled trial and one observational study: low.)
- Dosages and routes of administration for mifepristone followed by misoprostol
- Mifepristone should always be administered orally. The recommended dose is 200 mg.
- Administration of misoprostol is recommended 36 to 48 hours following ingestion of mifepristone.
 - The recommended dose of misoprostol is 800 µg vaginally.
 - Subsequent misoprostol doses should be 400 µg, administered either vaginally or sublingually, every 3 hours up to four further doses, until expulsion.
 - This recommendation is likely to be affected as studies are completed.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) specific to Mifeprex[®] (mifepristone). Local Coverage Determinations (LCDs) for Mifeprex[®] (mifepristone) do not exist at this time.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the [Medicare Benefit Policy Manual \(Pub. 100-2\), Chapter 15, section 50 Drugs and Biologicals](#). (Accessed March 22, 2018)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
06/01/2018	Policy updated per annual review. Approved by National Pharmacy & Therapeutics Committee on 05/18/2018. Policy 2017D0012M archived.
07/01/2017	Annual review. Removed "RU-486" from policy title. Added "in combination with misoprostol" to coverage rationale. Transferred to new policy template. Added Background section. Updated CMS statement and references. Approved by National Pharmacy & Therapeutics Committee on 04/26/2017. Policy 2016D0012L archived.
08/01/2016	Annual review. Increased GA to 70 days per FDA labelled indication. Updated CMS statement, Clinical Evidence, FDA, and references. Approved by National Pharmacy & Therapeutics Committee on 05/20/2016. Policy 2015D0012K archived.
10/01/2015	Updated Applicable Codes for ICD-10 transition. Policy 2015D0012J archived.
08/01/2015	Policy updated per annual review. Increased GA to 63 days. Updated CMS, Clinical Evidence, references. Approved by National Pharmacy & Therapeutics Committee on 05/20/2015. Policy 2014D0012I archived
08/01/2014	Policy updated per annual review. Updated references. Approved by National Pharmacy & Therapeutics Committee on 05/21/2014. Policy 2013D0012H archived.
07/01/2013	Policy updated per annual review. Added language to specify that mifepristone must be administered under the supervision of a qualified physician. Updated clinical evidence and references. Approved by National Pharmacy & Therapeutics Committee on 05/21/2013. Policy 2012D0012G archived.
07/01/2012	Policy updated per annual review. Added information regarding Korlym. Updated the list of unproven uses (removed refractory Cushing's disease and added induction of labor). Updated clinical evidence and references. Approved by National Pharmacy & Therapeutics Committee on 05/15/2012. Policy 2011D0012F archived.
07/01/2011	Policy updated per annual review. Approved by National Pharmacy & Therapeutics Committee on 05/10/2011. Policy 2010D0012E archived.
06/01/2010	Policy updated per annual review. Approved by National Pharmacy & Therapeutics Committee on 05/11/2010. Policy 2009D0012D archived.
07/14/2009	Policy updated. Approved by National Pharmacy & Therapeutics Committee on 06/9/2009. Policy 2008D0012C archived (7/21/2009).
09/10/2008	Policy updated. Approved by National Pharmacy & Therapeutics Committee on 06/10/2008. Policy 2006D0012B archived.