



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Mifepristone (Mifeprex[®])**

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Although mifepristone (Mifeprex[®], RU 486) is an oral medication, under benefit plans that provide coverage for elective abortion/termination of pregnancy, it is considered part of the medical benefit and is not a pharmacy benefit. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage for elective abortion.

If coverage is available for elective abortion, CIGNA covers mifepristone (Mifeprex[®], RU 486), as well as medically necessary associated services such as office visits, ultrasound studies and other medications, such as misoprostol, for the medical termination of early pregnancy.

CIGNA does not cover mifepristone (Mifeprex[®], RU 486) for any other indication, including as a morning-after pill (emergency contraception), because it is considered experimental, investigational or unproven.

General Background

Mifepristone, RU 486, or Mifeprex[®] (Danco Laboratories, LLC, New York, NY), is an oral medication indicated for the medical termination of early pregnancy, 49 days or less (i.e., seven weeks), counting from the beginning of the last menstrual period. Mifepristone induces an anti-progestational activity, which results from competitive interaction with progesterone at progesterone-receptor sites, inhibiting the action of endogenous or exogenous progesterone. Since progesterone is a key hormone in the establishment and maintenance of human

pregnancy, inhibiting its action results in termination of the pregnancy (U.S. Food and Drug Administration [FDA], 2009). Medical abortion mimics symptoms similar to those of spontaneous abortion (e.g., cramping and bleeding). The symptoms typically last for up to nine days, but in rare cases have been reported for as long as 45 days. Nausea, vomiting and diarrhea may also accompany the treatment. The reported success rate is 92%–97% if taken within 49 days of a woman's last menstrual period (LMP).

Mifepristone should be administered in a clinic, medical office or hospital, by or under the supervision of a physician. Medical abortion with mifepristone usually requires three office visits. It is recommended that prior to taking the medication, the patient should be appropriately counseled and sign a consent form indicating that she wants to terminate the pregnancy. Some states mandate a waiting period between the counseling and the initiation of the abortion. Therefore, there may be an additional office visit due to a state mandate.

Mifepristone is only distributed to physicians who can accurately determine the duration of a patient's pregnancy and detect an ectopic (i.e., tubal) pregnancy if present. Per the FDA, physicians who prescribe mifepristone must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or they must make plans in advance to ensure that care is available through an appropriate healthcare provider (FDA, 2007).

Mifepristone should not be confused with a morning-after pill or be used as a morning-after pill. Mifepristone is used to terminate a pregnancy while a morning-after pill is used to prevent a pregnancy (Planned Parenthood Federation of America, 2011).

U.S. Food and Drug Administration (FDA)

In September 2000, the FDA approved mifepristone for medical termination of early pregnancy, defined as 49 days or less, counting from the beginning of the last menstrual period. The FDA-approved administration regimen includes: 600 milligrams (mg) of oral mifepristone on day one; 400 micrograms (µg) of oral misoprostol, a prostaglandin, on day three; and a post-treatment follow-up on day 14 to confirm, by clinical examination and/or ultrasound, complete termination. The approval included strict guidelines for the administration of the drug, including patient education and obtained consent prior to its use (FDA, 2009; FDA, 2005).

The FDA approval was based on safety and efficacy data reported by three clinical trials. A United States trial included safety data on 859 women and efficacy data on 827 women, 49 days or less gestation dated from the LMP. The success rate was 92.1% (i.e., complete abortion occurred) with 6.3% of the study population experiencing expulsion within the first two days following administration of mifepristone alone. The women without expulsion were administered 400 µg of misoprostol two days after ingestion of mifepristone. Expulsion occurred in 44.1% of the women within four hours and 62.8% of the women within 24 hours. At the end of the study, 39 (4.7%) women had an incomplete abortion and eight (1%) had an ongoing pregnancy. Two French trials reported safety data on 1800 women and efficacy data on 1681 women. In these trials, 95.5% of women experienced complete abortion within two days of receiving 600 mg of mifepristone. Following administration of misoprostol, 50.3% expelled the products of conception within the first four hours, and 72.3% experienced expulsion within 24 hours following misoprostol administration (FDA 2005).

Other than termination of early pregnancy, mifepristone has not been approved by the FDA for any other indications.

Literature Review - Elective Abortion

Kulier et al. (2004) conducted a systematic review of 39 randomized controlled trials to compare the different medical methods for first trimester abortion. Four trials included the use of mifepristone 600 mg with prostaglandin compared to mifepristone 200 mg with prostaglandin. Oral misoprostol was reported less effective than vaginal misoprostol, and mifepristone alone was less effective than when used in combination with a prostaglandin. The authors concluded that safe and effective medical abortion is available and combined regimens were more effective than single agents.

Literature Review-Other Indications

Mifepristone has been proposed for use in multiple other indications, including the following: cancers (e.g., breast, endometrial, meningiomas and ovarian cancers); cervical preparation for surgical abortion; Cushing's syndrome; endometriosis; regular contraceptive (i.e., a daily or monthly dosage); second trimester abortion;

induction of labor; uterine fibroids or leiomyomas; and neuropsychiatric disorders (e.g., depression, anxiety disorders, Alzheimer's). Mifepristone is not FDA approved for any of these indications nor does the available data support the safety and efficacy of its use for these conditions (Check, et al., 2010; Dowswell, et al., 2010; Kapp, et al., 2010; Newmann, et al., 2010; Agarwal, et al., 2009; Blasey, et al., 2009; Hapangama, et al., 2009; Carbonell Esteve, et al., 2008; Johanssen and Allolio, 2007; Tang and Ho, 2007; Viswanathan, et al., 2007).

Bleeding Irregularities: In a randomized controlled trial, Engman et al. (2009) evaluated the effect of 50 milligrams of Mifepristone (n=14) compared to placebo (n=16) as a presurgical management in women with leiomyomas-related uterovaginal bleeding. The medication was administered every other day for 90 days prior to surgery. There was a significant decrease in the total leiomyomas volume (p=0.021) and number of bleeding days (p=0.001) and increase in serum hemoglobin (p=0.046) in the mifepristone group compared to the control group. Other outcomes showed no significant difference in the serum cortisol levels, a mild increase in serum androgen levels and no premalignant changes or changes in mitotic indices on endometrial biopsies. No adverse events were reported. The authors noted that "further studies are needed to understand the regulatory pathways and mechanisms involved in the size reduction of leiomyoma and the mechanism of action of mifepristone. A limitation of the study is the small patient population.

Weisberg et al. (2009) conducted a randomized controlled trial (n=204) to evaluate the effectiveness of mifepristone in Implanon users with prolonged and/or frequent bleeding episodes. Patients were equally randomized to one of five groups: 1) mifepristone 25 mg given twice on day one followed by four days of ethinyl estradiol (EE) 20 mg; (2) doxycycline 100 mg twice daily for five days; 3) mifepristone 25 mg given twice on day one plus doxycycline 100 mg twice daily for five days; (4) doxycycline 100 mg twice daily with EE 20 mg daily; and (5) placebo twice daily for five days. Mifepristone with EE or with doxycycline was more effective in stopping a bleeding episode (mean 4.0 days and 4.4 days, respectively) compared to doxycycline alone, doxycycline plus EE or placebo (mean 6.4 days, each). There was a significant difference in mifepristone plus EE and mifepristone plus doxycycline compared to placebo (p=0.0008, p=0.0108, respectively). Eight days after starting the first treatment, all women in the mifepristone plus EE group had stopped bleeding compared to 97% in the mifepristone plus doxycycline group, 65.6% in the doxycycline group, 60% in the doxycycline plus EE group and 70.3% in the placebo group. There were no significant differences between all the groups in the number of bleed-free days following treatment, duration of the first post-treatment bleed, number of bleeding/spotting days or episodes in the 90 day treatment or post-treatment phases or subsequent bleeding patterns. There were no serious adverse events reported. A limitation of the study is that 69 women were lost to final follow-up.

Abdel-Aleem et al. (2007) conducted a systematic review of the literature to evaluate preventive and therapeutic interventions used to normalize bleeding irregularities associated with the use of progestin-only contraceptives. Twenty-three randomized controlled trials met inclusion criteria. Four trials included the use of mifepristone for the purpose of controlling irregular bleeding that occurred as a result of using Norplant or an equivalent to Norplant. Overall, there was no significant difference in the decrease in bleeding with the use of mifepristone compared to the controls.

Cancer: Rocereto et al. (2010) evaluated the effectiveness and toxicity of mifepristone in 24 women with ovarian, peritoneal and fallopian tube cancers. Patients had persistent or recurrent cancer following chemotherapy. Oral mifepristone (200mg) was taken daily for 28 days. One woman had a partial response.

Emergency Contraception: Cheng et al. (2008) conducted a systematic review and meta-analysis of randomized controlled trials and controlled clinical trials to evaluate which emergency contraceptive methods used shortly after unprotected intercourse was the most effective, safe and convenient to prevent pregnancy. Eighty-one trials (n=45,842) met inclusion criteria. Methods included mifepristone middle dose (25–50 mg), mifepristone low dose (< 25 mg), two doses of levonorgestrel 0.75 milligrams, and copper intrauterine device (IUD). There were more pregnancies following the use of levonorgestrel compared to mifepristone mid-dose (25–50 mg) and mifepristone low dose (< 25 mg). Middle-dose mifepristone was more effective than other hormones. Delay in onset of subsequent menses was the main unwanted effect with the use of mifepristone and was related to the dosage. The IUD was effective and provided ongoing contraception. The authors proposed that mifepristone, levonorgestrel and the IUD were effective methods of emergency contraceptive. However, mifepristone is not FDA approved for use as an emergency contraceptive.

Fibroids: Feng et al. (2010) conducted a meta-analysis of two randomized controlled trials (n=62) to evaluate the effectiveness of mifepristone on health-related quality of life (HRQOL) in women with symptomatic fibroids.

The women were treated with mifepristone 5 mg or 2.5 mg or placebo. At six-months follow-up, a significant reduction in pain ($p<0.001$), bleeding ($p<0.001$), uterine size ($p=0.007$) and improvement in HRQOL ($p<0.001$) were reported. A limitation of the study is the small patient population.

Induction of Labor: Hapangama and Neilson (2009) conducted a systematic review of randomized controlled trials ($n=10$) to evaluate the effectiveness of mifepristone for cervical ripening for induction of labor. Compared to placebo, women treated with mifepristone were more likely to be in labor or to have a favorable cervix at 48 hours with the effect lasting to 90 hours. Mifepristone-treated women were less likely to undergo caesarean section, but had more instrumental deliveries. Treated women more often had abnormal fetal heart rate patterns, but there were no significant differences in neonatal outcomes. The evidence was insufficient to recommend the dosage and report the occurrence of uterine rupture or dehiscence.

Psychiatric Conditions: In a systematic review of randomized controlled trials comparing the use of antigluco-corticoid drugs (including mifepristone) to placebo or to an alternative drug treatment for mood episodes (i.e., manic, mixed affective or depressive), Gallagher et al. (2008) concluded that further investigation was needed to establish the clinical utility of the drugs. Nine studies met inclusion criteria, and four of the studies included the use of mifepristone. The authors noted that “considerable methodological differences” existed between the studies as it related to the compounds used and the patient population and that mifepristone should be considered at the “proof-of-concept stage” for the treatment of mood disorders and psychosis.

Professional Societies/Organizations

The American Cancer Society, the National Cancer Institute and the [®]National Comprehensive Cancer Network[®] do not discuss the use of mifepristone in the management of breast, epithelial or ovarian cancers.

In their 2005 (reaffirmed 2011) practice guideline on medical abortion, the American College of Obstetricians and Gynecologists (ACOG), recommended mifepristone as an acceptable means of medical abortion when administered according to the FDA-approved indications. ACOG also reports that clinical trials have investigated alternative dosage regimens for mifepristone and misoprostol in an effort to “reduce side effects, and to make medical abortion less expensive, safer, and more rapid”. The trials included comparisons of 200 mg of mifepristone to the FDA-approved 600 mg dosage, evaluation of the use of misoprostol 800 µg vaginally, timing between the administration of mifepristone and misoprostol, side effects of the proposed alternative dosage (200 mg mifepristone and 800 µg misoprostol), and analysis of complete abortion rates. Based upon their review of these trials, ACOG stated “compared with the FDA-approved regimen, mifepristone–misoprostol regimens using mifepristone, 200 mg orally, and misoprostol, 800 µg vaginally, are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP”.

Summary

Mifepristone is a medical abortion agent that has been shown to be a safe and effective method of medical termination of early pregnancy when administered in accordance with the FDA-approved guidelines. Adverse events reported with the use of the drug have included serious bacterial infection, bleeding, ruptured ectopic pregnancies and death from sepsis. Patients should be informed of the risks prior to consenting to the therapy, and providers should be aware of reported complications, especially post-treatment infections.

The evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of mifepristone for any other indications, including as a “morning after pill” or for the treatment of abnormal uterovaginal bleeding, fibroids, cancer, labor induction, or psychiatric conditions. Overall, studies have primarily included small patient populations, short-term follow-ups and inconsistent methodology with no significant improvements in outcomes. Mifepristone is not approved by the US Food and Drug Administration for any indications other than the termination of early pregnancy.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
S0190	Mifepristone, oral, 200 mg
S0191	Misoprostol, oral, 200 mcg
S0199	Medically induced abortion by oral ingestion of medication including all associated services and supplies (e.g., patient counseling, office visits, confirmation of pregnancy by HCG, ultrasound to confirm duration of pregnancy, ultrasound to confirm completion of abortion) except drugs

ICD-9-CM Diagnosis Codes	Description
635.80	Unspecified legally induced abortion with unspecified complication
635.81	Incomplete legally induced abortion with unspecified complication
635.82	Complete legally induced abortion with unspecified complication
635.90	Legally induced abortion without mention of complication, unspecified
635.91	Incomplete legally induced abortion without mention of complication
635.92	Legally induced abortion without mention of complication, complete
637.92	Legally unspecified abortion, complete, without mention of complication
V22.2	Pregnant state, incidental
V61.7	Other unwanted pregnancy

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
626.0-626.9	Disorders of menstruation and other abnormal bleeding from female genital tract
632	Missed abortion
V25.03	Encounter for emergency contraceptive counseling and prescription

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	8/15/2007	0134	Mifepristone (RU 486)

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CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.