MIFEPRISTONE (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾HS109

Commonly used brand name(s):Mifeprex.
Another commonly used name is RU 486.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Abortifacient.

Indications

Accepted

Abortion¾Mifepristone is indicated in combination with misoprostol for the medical termination of intrauterine pregnancy of 49 days' duration or less. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾429.6 1

Mechanism of action/Effect:

Mifepristone competitively inhibits the actions of progesterone at progesterone-receptor sites, resulting in termination of pregnancy. 1 The combination of mifepristone and misoprostol causes expulsion of the products of conception through decidual necrosis, myometrial contractions, and cervical softening. 1

Absorption:

The absolute bioavailability of oral mifepristone is 69% 1

Protein binding:

Very high (98%); predominantly to albumin and alpha 1- acid glycoprotein. 1

Biotransformation:

Hepatic, by Cytochrome P450 3A4 isoenzyme to the N-monodemethylated metabolite (RU 42 633); RU 42 698, which results from the loss of two methyl groups from position 11 beta; and RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain. 1

Half-life:

Terminal ¾ 18 hours; begins slowly and becomes more rapid with time. 1

Time to peak concentration:

90 minutes after a 600 mg oral dose. 1

Peak plasma concentration:

1.98 mg/L following a single 600 mg oral dose. 1

Elimination:

Fecal; 83% of a 600 mg dose over 11 days. 1

Renal; 9% of a 600 mg dose over 11 days. 1

Precautions to Consider

Carcinogenicity

Studies in humans or animals have not been done. 1

Mutagenicity

Mifepristone was not found to be mutagenic in multiple assays, including the Ames test, Saccharomyces cerevisiae D4 cell conversion test, and Schizosaccharomyces pompe P1 cell forward mutation test. No positive results were noted during tests designed to induce chromosomal damage, including induction of chromosome aberrations in CHO cells, induction of genetic damage in V79 Chinese hamster lung cells, and the mouse micronucleus assay. 1

Pregnancy/Reproduction

Fertility¾Mifepristone necessarily disrupts the estrus cycle, however, it did not appear to have an effect on long term fertility in rats given 0.3 mg per kg per day orally. Administration of up to 100 mg per kg did not affect the future reproductive capabilities of rats given the drug on the day after birth. In one study, rats given mifepristone 1 mg every other day as neonates were noted to have oviduct and ovary malformations, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency. 1

Pregnancy¾Mifepristone is used to terminate intrauterine pregnancy and has no other use during pregnancy. 1

Other prostaglandins, including misoprostol, have been reported to be teratogenic in human beings. Skull defects, cranial nerve palsies, delayed growth, delayed psychomotor development, facial malformation, and limb defects have been reported following exposure to prostaglandins in the first trimester. 1

Mifepristone administration at doses equivalent to one-sixth the normal human exposure to rabbits resulted in skull deformities, but studies in mice and rats have revealed no teratogenic effects. 1

Breast-feeding

It is unknown whether mifepristone is distributed into breast milk. 1

Pediatrics

No information is available. Safety and efficacy have not been established.

Geriatrics

There is no appropriate use of mifepristone in the geriatric population.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Anticoagulant therapy

(excessive bleeding may occur 1)

>> Corticosteroid therapy, long-term, concurrent 1

>> Cytochrome P450 enzyme inducers, including:
Carbamazepine

Dexamethasone

Phenobarbital

Phenytoin

Rifampin

St. John's Wort

(although specific interaction studies have not been performed, it is likely the metabolism of mifepristone will be induced, resulting in decreased serum levels of mifepristone 1)

>> Cytochrome P450 enzyme inhibitors, including:
Erythromycin

Grapefruit juice

Itraconazole

Ketoconazole

(although specific interaction studies have not been performed, it is likely the metabolism of mifepristone will be inhibited, resulting in increased serum levels of mifepristone 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Hemorrhagic disorder

(excessive bleeding may occur 1)

>> Adrenal failure, chronic 1

>> Ectopic pregnancy or

>> Undiagnosed adnexal mass

(treatment procedure will not terminate ectopic pregnancy 1)

>> Hypersensitivity to mifepristone, misoprostol or other prostaglandins 1

>> Intrauterine device (IUD)

(IUD must be removed prior to initiation of treatment procedure 1)

>> Porphyria, inherited 1

Risk-benefit should be considered when the following medical problems exist

Anemia, severe or

Hemostatic disorders or

Hypocoagulability

(mifepristone causes heavy bleeding in a small portion of users, care should be exercised 1)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Clinical examination or

Ultrasonagraphic scan

(should occur 14 days after mifepristone administration to confirm termination of pregnancy and assess bleeding; pregnancy test for HCG may not be reliable at this time 1)

Hematocrit and

Hemoglobin concentration and

Red blood cell count (RBC)

(mifepristone caused hemoglobin decreases greater than 2 gm/deciliter in clinical trials 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Decrease in hemoglobin concentration 1 (unusual tiredness or weakness)¾ occurred at a rate of 6% in French trials only; uterine hemorrhage 1 (excessively heavy vaginal bleeding) 1

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain or uterine cramping 1; back pain 1; diarrhea 1; dizziness 1; fatigue 1 (unusual tiredness or weakness); headache 1; nausea and vomiting 1

Incidence less frequent

Anemia 1 (pale skin; troubled breathing, exertional; unusual bleeding or bruising; unusual tiredness or weakness); anxiety; asthenia 1 (lack or loss of strength); dyspepsia 1 (acid or sour stomach ; belching ; heartburn ; indigestion ; stomach discomfort, upset, or pain); fever 1;

insomnia 1 (sleeplessness or trouble sleeping); leg pain 1; leukorrhea 1 (increased clear or white vaginal discharge); rigors 1 (shaking chills); sinusitis 1 (pain or tenderness around eyes and cheekbones; fever ; stuffy or runny nose ; headache; cough; shortness of breath or troubled breathing; tightness of chest or wheezing); syncope 1 (fainting or light-headedness when getting up from a lying or sitting position); vaginitis 1 (itching of the vagina or genital area; pain during sexual intercourse; thick, white vaginal discharge with no odor or with a mild odor); viral infection 1 (chills ; cough or hoarseness fever ; cold ; flu-like symptoms)

Overdose

For more information on the management of overdose or unintentional ingestion, contact a poison control center (see Poison Control Center Listing).

Treatment of overdose

There is no known specific antidote to mifepristone. Treatment is generally symptomatic and supportive.
Patients ingesting a massive overdose should be closely observed for signs of adrenal failure. 1

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Mifepristone (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to mifepristone, misoprostol or other prostaglandins
Pregnancy¾Increased risk of fetal malformation if treatment procedure is not successful in terminating pregnancy
Other medications, especially anticoagulants, corticosteroids, hepatic enzyme inducers, hepatic enzyme inhibitors
Other medical problems, especially adrenal failure, hemorrhagic disorders, ectopic pregnancy or undiagnosed adnexal masses, intrauterine devices in place, porphyria (inherited)
Proper use of this medication

>> Proper dosing
Precautions while using this medication

>> Consulting physician if bleeding seems excessive or prolonged

Follow-up

>> Three visits to physician, including follow-up visit 14 days after mifepristone administration

Advisability of surgical termination if medical abortion is not successful

Side/adverse effects

Signs of potential side effects, especially decrease in hemoglobin concentration or uterine hemorrhage

General Dosing Information

Patients receiving mifepristone should be under supervision of a physician who has read and understood the prescribing information. 1

Patients may only receive mifepristone directly from a physicians office which has registered with the manufacturer and has signed the Prescribers Agreement. The drug is not available through pharmacies. 1

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement. 1

Treatment with mifepristone and misoprostol to terminate pregnancy requires 3 office visits by the patient. 1

Treatment protocol is:
· Day One ¾ Mifepristone is administered to the patient in physician's office. 1

· Day Three ¾ Unless expulsion of products of conception has already occurred, misoprostol is administered to the patient in the physician's office. 1

· Day Fourteen ¾ Patient returns for clinical exam to verify termination of pregnancy. 1

Surgical termination of the pregnancy is recommended following medical abortion treatment failure due to the risk of fetal malformation with prostaglandins. 1

Oral Dosage Forms

MIFEPRISTONE TABLETS

Usual Adult Dose

Abortifacient¾
Oral, 600 mg (three 200 mg tablets) as a single dose on day one, followed on day three by 400 mcg (two 200 mcg tablets) of misoprostol as a single dose, if abortion has not yet occurred. 1

Usual Pediatric Dose

Safety and efficacy have not been established.

Usual Geriatric Dose

Safety and efficacy have not been established.

Strength(s) usually available
U.S.¾200 mg (Rx)[Mifeprex (colloidal silica anhydrous) (corn starch) (magnesium stearate) (microcrystalline cellulose) (povidone)]

Packaging and storage:

Store at 25 °C (77 °F), in a tight container. Protect from light. 1

Additional information:

Tablets are packaged in a blister package containing 3 tablets, supplied in individual cartons. 1

Product is not available through pharmacies.