PRODUCT INFORMATION – Mifepristone Linepharma 200 mg Tablet

This medication is only for use in termination of pregnancy for medical reasons beyond the first trimester. Medical termination of pregnancy up to 63 days gestation requires the use of MS-2 Step (mifepristone, misoprostol).

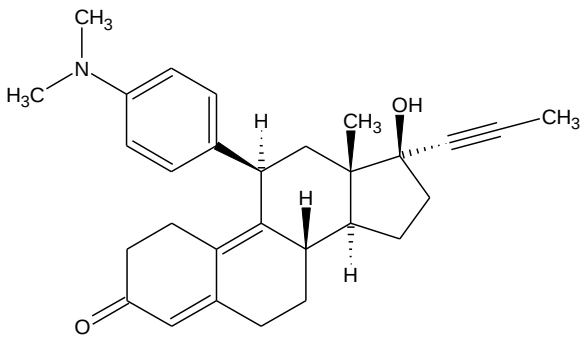
This medication should only be prescribed by medical practitioners with appropriate obstetric qualifications and training to provide termination of pregnancy beyond the first trimester. Published guidelines should be consulted for appropriate prostaglandin regimens that should only be provided in appropriately equipped facilities. It is important that all patients receiving this medication are followed up by a medical practitioner to ensure the medication has been effective. Even if no adverse events have occurred all patients must receive follow up after taking mifepristone. Read the SPECIAL WARNINGS AND PRECAUTIONS FOR USE carefully.

Name of the Medicine

Mifepristone Linepharma 200 mg Tablet

Australian Approved Name (AAN): Mifepristone

Chemical Structure:



Molecular formula: $C_{29}H_{35}NO_2$ Molecular weight: 429.6

CAS Registry Number: 84371-65-3

Description

White to off-white, round biconvex tablets, diameter 11 mm, with MF debossed on one side of the tablet.

Each tablet contains 200 mg of mifepristone.

Mifepristone Linepharma 200 mg tablet contains the following excipients: maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Pharmacology

Pharmacodynamic properties

Pharmacotherapeutic group: Other Sex Hormone and Modulator of the Reproductive function/ Antiprogestogen. ATC code: GO3XB01

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species (rat, mouse, rabbit, dog and monkey). This action is manifested in the form of pregnancy termination.

In women at doses of greater than or equal to 1 mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

Mifepristone binds to the glucocorticoid receptor with affinity comparable to that for the progesterone receptor. Full inhibition of the action of dexamethasone was evident in rats at oral doses 0.5-1.1 times the human dose adjusted for body surface area. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone also has some anti-androgenic activity. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

Pharmacokinetic properties

Absorption

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half life of mifepristone is 36.5 to 38.3 hours.

Mifepristone shows non-linear pharmacokinetics. Following the distribution phase the elimination is at first slow, with a half-life of approximately 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

Distribution

In plasma, mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, the volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

Metabolism and excretion

N mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Plasma AUC for the dominant metabolite, monodemethylated mifepristone, is approximately double that of the unchanged mifepristone at the clinical dose, and this metabolite retains significant affinity for the progesterone receptor. The other metabolites also display some progesterone receptor affinity (approximately 10 to 15% that of mifepristone). The metabolites may contribute to the pharmacological effects of mifepristone.

In vitro CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77%. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1) had apparently no action on mifepristone metabolism.

After administration of 600 mg radiolabeled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

Clinical trials

In clinical trials the results vary slightly according to the prostaglandin analogue used and the time of application.

Evidence based guidelines and reviews should be consulted for prostaglandin regimens to be used for termination beyond the first trimester. Failures are due to retained placenta or

incomplete abortion and may necessitate a surgical procedure to complete the abortion process.

For termination of pregnancy beyond first trimester, pretreatment with 200 mg mifepristone facilitates the procedure: the induction to abortion interval is reduced, as well as the need for prostaglandin analogues (gemeprost or misoprostol). Several studies report prostaglandin regimens used in the gestation range of 12-24 weeks associated with median induction-abortion intervals in the range of 5-8 hours and over 90% of women aborting within 24 hours[1,2,3,4,5]. Surgical evacuation was needed in 10-12%, with some studies reporting as high as 20-30%[6,7,8,9].

Indications

Mifepristone Linepharma 200 mg tablet is indicated in females of childbearing age for:

Preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

[1] Thong KJ. Baird DT. A study of gemeprost alone, dilapan or mifepristone in combination with gemeprost for the termination of second trimester pregnancy. Contraception 1992, 46, 11-7

[2] Ho PC. Chan YF. Lau W. Misoprostol is as effective as gemeprost in termination of second trimester pregnancy when combined with mifepristone: a randomised comparative trial. Contraception 1996, 53, 281-3

[3] Ho PC. Ngai SW. Liu KL. Wong GC. Lee SW. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstetr Gynecol 1997, 90, 735-8

[4] Tang O.S. Thong K.J. Baird D.T. Second trimester medical abortion with mifepristone and gemeprost: A review of 956 cases. Contraception 2001, 64, 29-32

[5] Webster D. Penney GC. Templeton A. A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. Br J Obstetr Gynecol 1996, 103, 706-9

[6] Bartley J. Baird DT. A randomised study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. Br J Obstetr Gynecol 2002, 109, 1290-4

[7] Ngai SW. Tang OS. Ho PC. Randomized comparison of vaginal (200 microg every 3 h) and oral (400 microg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. Human Reprod 2000, 15, 2205-8

[8] Tang OS. Chan CC. Kan AS. Ho PC. A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12-20 weeks gestation. Human Reprod 2005, 20, 3062-6

[9] Tang O.S. Thong K.J. Baird D.T. Second trimester medical abortion with mifepristone and gemeprost: A review of 956 cases. Contraception 2001, 64, 29-32

Contraindications

This product should not be prescribed in the following situations:

- Lack of access to emergency medical care until complete expulsion is recorded;
- Suspected or confirmed ectopic pregnancy;
- Uncertainty about gestational age;
- Chronic adrenal failure;
- Concurrent long term corticosteroid therapy;
- Suspected or known haemorrhagic disorders or treatment with anti-coagulants;
- Hypersensitivity to mifepristone, the prostaglandin analogue to be used, or any of the excipients;
- Contraindication to the prostaglandin analogue selected.

Precautions

This medication is for use in termination of pregnancy for medical reasons beyond the first trimester. Medical termination of pregnancy up to 63 days gestation requires the use of MS-2 Step (mifepristone, misoprostol).

Mifepristone Linepharma (or the prostaglandin analogue) should be used with caution if an intrauterine device is present. If it can be removed safely first, this should be done.

Due to the antiglucocorticoid activity of mifepristone, take special care in case of suspected acute adrenal failure. In addition, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

The precautions related to the prostaglandin analogue used should be followed where relevant.

Rare serious cardiovascular accidents have been reported following administration of prostaglandins. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Special warnings and precautions for use

- *Populations not studied:*
  In the absence of specific studies, Mifepristone Linepharma is not recommended in patients with:
  - Cardiovascular disease

- Hypertensive disease
- Hepatic disease
- Respiratory disease
- Renal disease
- Diabetes
- Severe anaemia
- Malnutrition
- Heavy smokers
- Women who are older than 35 years and who also smoke 15+ cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

- *Precautions*

  - This medication should only be prescribed by medical practitioners with appropriate obstetric qualifications and training to provide termination of pregnancy beyond the first trimester.

  - Published guidelines should be consulted for appropriate prostaglandin regimens that should only be provided in appropriately equipped facilities.

  - Ectopic pregnancy

Ectopic pregnancy should be excluded and gestation confirmed prior to medical abortion.

  - Rhesus alloimmunisation

The use of Mifepristone Linepharma requires rhesus determination and hence the prevention of rhesus alloimmunisation.

  - Explanation of requirements for the method

This method requires the involvement of the woman who should be informed of the requirements of the medical method, which involves:

- The necessity to combine treatment with a prostaglandin analogue
- The need to adhere to treatment protocols and for follow-up after intake of Mifepristone Linepharma
- The risk of failure of the medical method which may require completion of the termination by another method.
- On discharge from the treatment centre all women should be fully counseled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access.

The expulsion may take place before prostaglandin administration. Local protocols should be in place to manage this occurrence. This does not preclude the need for follow-up to confirm complete expulsion.

The following risks related to the medical method must be taken into account and explained to the woman:

- Failures

The non-negligible risk of failure, including retained placenta and incomplete abortion, which may require completion of the termination by another method.

- Bleeding

The patient must be informed of the potential for bleeding prior to the administration of the selected prostaglandin which in no way precludes the need to adhere to treatment protocols and follow up. Bleeding post-expulsion in the second trimester may lead to a significant decrease in haemoglobin levels and can be large enough to necessitate a blood transfusion in around 0.5% of women.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. The patient must receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

Follow-up as per local protocols must take place after administration of Mifepristone Linepharma and expulsion of the conceptus. Persistence of vaginal bleeding could signify incomplete abortion and appropriate treatment should be arranged.

Since heavy or prolonged bleeding requiring haemostatic curettage occurs in up to 5 % of cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

- Infection

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 mifepristone. Doctors evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a fever, 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 (from e.g. *Clostridium sordellii* or other species e.g. *Streptococcus*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking mifepristone and a prostaglandin. 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, haemoconcentration, and generally feeling tired or unwell. Most of these deaths occurred in women who used vaginally administered misoprostol however other forms of administration have been reported. No causal relationship between mifepristone and prostaglandin use and an increased risk of infection or death has been established. *Clostridium sordellii* and other infections such as *Streptococcus* and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in

other gynaecologic and non-gynaecolgic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

Following abortion, women must be given a written account of the symptoms they may experience and a list of those that would make an urgent medical consultation necessary. They should be given a 24-hour telephone helpline number to use if they feel worried about pain, bleeding or high temperature. Urgent clinical assessment and emergency gynaecology admission must be available when necessary. On discharge, each woman should be given a letter that gives sufficient information about the procedure to allow another practitioner elsewhere to deal with any complications.

Effects on fertility

Mifepristone inhibited oestrus cycling in rats at oral doses of 0.3-1 mg/kg/day (less that the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after Mifepristone Linepharma administration.

Use in pregnancy

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

Foetal skull/brain malformations, presumed to be related to treatment, have been observed in rabbits and monkeys, but not mice or rats, treated with sub-abortive doses of mifepristone. These most likely occurred secondary to mifepristone's effect on the uterus due to antagonism of progesterone.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated with the prostaglandin analogue. Therefore, data are too limited to determine whether the molecule is a human teratogen.

Should the patient wish to continue with her pregnancy following the administration of Mifepristone Linepharma, the available data are too limited to justify a systematic termination of an exposed pregnancy. In that event, careful ultra-sonographic monitoring of the pregnancy should be carried out.

Use in lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data is available. Consequently, Mifepristone Linepharma use should be avoided during breast-feeding.

Paediatric use

Limited data are available for use of Mifepristone Linepharma in women under 18 years.

There is no relevant use of Mifepristone Linepharma in the prepubertal paediatric population in the indications.

Use in the elderly

There is no relevant use of Mifepristone Linepharma in the elderly population in the indications.

Genotoxicity

Mifepristone has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells; gene conversion in yeast; unscheduled DNA synthesis in HeLa cells; and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity

No long-term animal carcinogenicity studies have been conducted with mifepristone. Based on the negative genotoxicity results, findings in general repeat-dose toxicity studies and considering the pattern of clinical use, mifepristone is not predicted to pose a particular carcinogenic risk.

Interactions with other medicines

No interaction studies have been performed.

On the basis of mifepristone’s metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* information showing that mifepristone acts as a mechanism-based inhibitor of CYP3A4, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the irreversible nature of the CYP binding and 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 CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Adverse effects

There are limited safety data from experience with use of mifepristone in medical terminations beyond the first trimester. The adverse events reported with mifepristone use in first trimester terminations with the prostaglandin analogues misoprostol or gemeprost, classified according to frequency and system organ class, are summarised as shown in Table 1.

Table 1: Adverse Events for the Combined Use of Mifepristone and Misoprostol or Gemeprost				
MedDRA	**Adverse events (frequency)**			
System Organ Class	**Very common** ≥ **1/10**	**Common** ≥ **1/100 to < 1/10**	**Uncommon** ≥ **1/1000 to < 1/100**	**Rare** ≥ **1/10000 to < 1/1000 and very rare (< 1/10000)***
Infections and infestations			Infection	Toxic shock syndrome
Neoplasms benign, malignant and unspecified				Elevated alpha-foeto protein Elevated carcinoembryonic antigen
Blood and lymphatic system disorders				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus
Psychiatric disorders				Mania
Nervous system disorders	Headache			Epilepsy Neurogenic tinnitus
Eye disorders				Ophthalmoplegia
Cardiac disorders				Myocardial infarction Induced Adam-Stokes syndrome
Vascular disorders			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis
Respiratory, thoracic and mediastinal disorders				Bronchospasm Induced bronchial asthma
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding Necrotising pancreatitis

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System Organ Class	**Very common** ≥ **1/10**	**Common** ≥ **1/100 to < 1/10**	**Uncommon** ≥ **1/1000 to < 1/100**	**Rare** ≥ **1/10000 to < 1/1000 and very rare (< 1/10000)***
Hepatobiliary disorders				Abnormal liver function tests Hepatic failure Hepatorenal failure
Skin and subcutaneous tissue disorders			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*
Musculoskeletal and connective tissue disorders				Limb spasm
Renal and urinary disorders				Renal failure
Pregnancy, puerperium and perinatal conditions	Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.	Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases.		Hydatiform mole Ectopic pregnancy Amniotic band syndrome Gestational trophoblastic tumor Uteroplacental apoplexy
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe haemorrhage Endometritis Breast tenderness Heavy bleeding	Haemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Haematosalpynx Uterine rupture
General disorders and administration site conditions	Fatigue Chill / fever Dizziness	Fainting		Anaphylaxis Periorbital edema Vagal symptoms

*Including occasional case reports

- Post-marketing experience for first trimester termination of pregnancy indicates that death can occur as a result of medical termination of pregnancy (although this is a very rare outcome, <1 in 100,000). The reported deaths were due to sepsis (fatal toxic shock syndrome) associated with Clostridium sordellii, which also occurs in association with childbirth and spontaneous termination. The symptoms of Clostridium sordellii infection are sometimes not the usual symptoms of sepsis. Therefore, the possibility of sepsis should be considered in all women who present with nausea, vomiting, or diarrhoea and weakness, with or without abdominal pain following mifepristone/prostaglandin use. These symptoms, even without a fever, may indicate Clostridium sordellii infection. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and haemo-concentration may be indicative of sepsis. Practitioners should consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii. No causal relationship between mifepristone and prostaglandin use and an increased risk of infection or death has been established. Clostridium sordellii and other infections such as Streptococcus and other bacteria have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynaecologic and non-gynaecolgic conditions. Reviews have estimated overall serious infection rates after medical abortion at less than 1%.

- Bleeding is an almost constant part of the procedure, whatever the prostaglandin analogue used. It can occur after mifepristone alone. When heavy, it usually reflects incomplete abortion: in clinical trials surgical evacuation was needed in 10-12% of women, with some studies reporting a rate as high as 20-30%. It can be prolonged for several days after prostaglandin analogue administration and sometimes leads to a decrease in haemoglobin levels. The degree of bleeding can necessitate a blood transfusion in around 0.5% of patients in the second trimester.

Dosage and administration

Preparation for the action of prostaglandin analogues during the termination of pregnancy for medical reasons beyond the first trimester.

The method of administration is as follows:

200 mg of mifepristone (1 tablet containing 200 mg) orally, followed 36 to 48 hours later by the scheduled prostaglandin analogue administration, which will be repeated as often as indicated.

No studies have been conducted on the effect of food intake on the absorption of mifepristone. It is recommended that Mifepristone Linepharma should not be taken within 2 hours of a meal.

Overdosage

No case of overdose has been reported.

In the event of massive ingestion signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

Presentation and storage conditions

PVC/PVDC/Aluminium blister of 1 tablet

Pack size of 1 tablet

Store below 30°C.

Keep in the original carton in order to protect from light

Keep out of reach of children

Name and address of the sponsor

MS Health

Suite 129, 135 Cardigan Street

Carlton VIC 3053

Australia

Licensed from Linepharma International Limited (UK).

Poison schedule of the medicine

Schedule 4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

29 August 2012

Date of most recent amendment

12 May 2015

The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation.