New Zealand Data Sheet

MIFEGYNE

Mifepristone micronised 200 mg tablets

Active substance	Mifepristone micronised	200 mg
Excipients or other ingredients (all of mineral or vegetable origin)	Anhydrous colloidal silica	3 mg
	Maize starch	102 mg
	Povidone	12 mg
	Microcrystalline cellulose	30 mg
	Magnesium stearate	3 mg

Presentation

Light yellow, cylindrical, bi-convex tablets, for oral administration. Blister pack (PVC and aluminium foil and carton) containing 3 tablets of Mifegyne 200 mg. Medicines classification: Prescription medicine.

Uses

Actions

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. In pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandin. It is an abortifacient. It does not bind to mineralocorticoid receptors; therefore the risk of acute adrenal failure during mifepristone intake is negligible. It binds to the glucocorticoid receptors. In animals at doses of 10-25 mg/kg it inhibits the action of dexamethasone. 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.

It has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

Pharmacokinetics

After oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/ml is reached after 1.3 hrs (mean of 10 subjects). There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hrs and then more rapidly, giving an elimination half-life of 18 hrs. With radio receptor assay techniques, the terminal half-life is up to 90 hrs, including all metabolites of mifepristone able to bind to progesterone receptors. After administration of low doses of mifepristone (20 mg orally or intravenously) the absolute bioavailability is 69%. In plasma, mifepristone is 98% bound to plasma proteins:

albumen and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG. N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. After administration of a 600 mg labelled dose of mifepristone, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces. Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk.

Indications

1. As a medical alternative to surgical termination of intra-uterine pregnancy
2. Softening and dilatation of the cervix uteri prior to surgical pregnancy termination
3. Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons
4. Labour induction for the expulsion of a dead fetus (fetal death in utero).

Dosage and Administration

There are no precautions for timing in relation to food.

1. As a medical alternative to surgical termination of intra-uterine pregnancy in early pregnancy: 600 mg mifepristone (3 tablets) in a single oral dose followed 36-48 hrs later, by the administration of a prostaglandin analogue; misoprostol 400 mcg orally (up to 49 days).
2. Softening and dilatation of the cervix uteri prior to surgical pregnancy termination: 200 mg mifepristone (one tablet), followed 36-48 hrs later (but not beyond) by a surgical termination of pregnancy.
3. Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons (to reduce the doses of prostaglandin): 600 mg of mifepristone (3 tablets) taken in a single oral dose, 36-48 hrs prior to scheduled prostaglandin administration which will be repeated as often as indicated.
4. Labour induction for expulsion of a dead fetus (fetal death in utero): 600 mg of mifepristone in a single oral daily dose for 2 consecutive days. Mifegyne alone leads to expulsion in about 60%. Labour should be induced by the usual methods if it has not started within 72 hrs following the first administration of mifepristone.

Contraindications

This product SHOULD NEVER be prescribed in the following situations.

IN ALL INDICATIONS

- chronic adrenal failure,

- hypersensitivity to the active substance or to any of the excipients,
- severe asthma uncontrolled by therapy,
- inherited porphyria.

In the indication: medical termination of developing pregnancy

- pregnancy not confirmed by ultrasound scan or biological tests,
- pregnancy beyond 63 days of amenorrhea,
- suspected extra-uterine pregnancy,
- contra-indication to the prostaglandin analogue selected.

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:

- pregnancy not confirmed by ultrasound scan or biological test,
- pregnancy of 84 days of amenorrhea and beyond
- suspected extra-uterine pregnancy.

Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*

- contra-indications to the prostaglandin analogue selected

Labour induction in foetal death in utero

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

Warnings

In the absence of specific studies, Mifegyne is not recommended in patients with:
- ***Renal failure***
- ***Hepatic failure***
- ***Malnutrition***

1. Medical termination of developing intra-uterine pregnancy

This method requires an active involvement of the woman who should be informed of the method's requirements:

- the necessity to combine treatment with prostaglandin to be administered at a second visit,
- the need for a follow-up visit (3rd visit) within 14 to 21 days after intake of Mifegyne in order to check for complete expulsion,
- the possible failure of the method, leading to a pregnancy termination by another method.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifegyne.

The expulsion may take place before prostaglandin administration (in about 3% of cases).

This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

Risks related to the method

- Failures

The non-negligible risk of failure, which occurs in 1.3 to 7.5 % of the cases, makes the control visit mandatory in order to check that the expulsion is completed.
In rare case of non complete expulsion, a surgical revision may be necessary.

The efficacy of the method decreases with parity, and consequently increasing age of the woman.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 12 days or more after Mifegyne intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will 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.

A follow-up visit must take place within a period of 14 to 21 days after administration of Mifegyne to verify by the appropriate means (clinical examination, ultrasound scan, and beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.
If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.

In the event of an ongoing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.

Since heavy bleeding requiring haemostatic curettage occurs in 0 to 1.4% of the 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 or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder and the level of anaemia.

- Infection

Very rare cases of fatal or serious toxic shock caused by pathogens like Clostridium sordellii endometritis, Escherichia coli, presenting with or without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication.

2. Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of Mifegyne must be followed, 36 to 48 hours later and not beyond, by surgical termination.

Risks related to the method

- Bleeding
  The woman will be informed of the risk of vaginal bleeding which may be heavy, following intake of Mifegyne. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.
  Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with haemostatic disorders, hypocoagulability, or severe anaemia.

- Other risks
  They are those of the surgical procedure.

3. In all instances

The use of Mifegyne requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.
During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.
To avoid 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 administration.

Precautions

1. In all instances

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of mifepristone.

Due to the antiglucocorticoid activity of mifepristone, 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 Mifegyne. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

2. Medical termination of developing intra-uterine pregnancy

Rare but serious cardiovascular accidents have been reported following the intra muscular administration of prostaglandin analogue. For this reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Method of prostaglandin administration

During intake and for three hours following the intake, the patient should be monitored in the treatment centre, in order not to miss possible acute effects of prostaglandin administration. The treatment centre must be equipped with adequate medical facilities.

On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access.

3. For the sequential use of Mifegyne - Prostaglandin, whatever the indication

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

4. Fertility, pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.
With subabortive doses, isolated cases of malformations are observed in rabbits, but not in rats or mice, and are too few to be considered significant, or attributable to mifepristone.
In clinical practice, rare cases of malformations of the extremity of lower limbs (out of them, club-foot) have been reported in case of mifepristone administered alone or associated with prostaglandins. However, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultrasound monitoring of the pregnancy will be established, with a special attention to the limbs.

Lactation
Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

5. Effects on ability to drive and to use machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse Effects

Nervous system disorders
Rare:
- Headache

Gastrointestinal disorders
Very common:
- Nausea, vomiting, diarrhoea (these gastro intestinal effects related to prostaglandin use are frequently reported).
Common:
- Cramping, light or moderate.

Skin and subcutaneous tissue disorders
Uncommon:
- Hypersensitivity: Skin rashes uncommon (0.2%).
Rare
- Single cases of urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis have also been reported.
Very rare:
- Angioedema

Infections and infestations
Common:
- Infection following abortion. Suspected or confirmed infections (endometritis, pelvic inflammatory disease) have been reported in less than 5% of women.
Very rare:
- Very rare cases of serious or fatal toxic shock caused by pathogens like *Clostridium sordellii* endometritis or Escherichia coli, presenting with or without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication (see section 4.4. – special warnings and special precautions for use).

Vascular disorders
Uncommon:
- Hypotension (0.25%)

General disorders and administration site conditions
Rare:
- malaise, vagal symptoms (hot flushes, dizziness, chills), fever.

Reproductive system and breast disorders
Very common:
- Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
Common:
- Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases.
Rare:
- During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during the third trimester, uterine rupture has been uncommonly

reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

Interactions

No interaction studies have been performed. On the basis of this drug'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 invitro inhibition information, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interactions 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 anaesthesia.

A decrease of the efficacy of the prostaglandin can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs including aspirin. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

Overdosage

Single doses of mifepristone up to 2G caused no unwanted reaction. In the event of massive ingestion, signs of adrenal failure might occur. Acute intoxication may require admission to hospital and if relevant treatment with dexamethasone.

Pharmaceutical Precautions

No known incompatibilities.

Shelf life 4 yrs

Medicine Classification

Prescription medicine.

Further Information

Mifegyne must only be used in accordance with the legislation governing termination of pregnancy. It must be prescribed by a doctor and administered by a health professional in a licensed premise. It will not be available through pharmacies.

Name and Address

Istar Ltd
8 Braithwaite St
Karori
Wellington.

Phone: (04) 476 8112

Fax: (04) 476 6380

Date of Preparation

3 July 2013