If MIFEGYNE® results in incomplete abortion, surgical intervention may be necessary. Medical practitioners must give patients clear instructions on the process to be followed in the event of an emergency following administration of MIFEGYNE®.

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MIFEGYNE ® 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg mifepristone.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Cylindrical, biconvex, light-yellow tablets, about 11 mm in diameter with an identification code on one face (167B).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Medical alternative to surgical termination of intra-uterine pregnancy of up to 56 days after the first day of the last menstrual period and/or ultrasound scan, in combination with a prostaglandin analogue.
2. Softening and dilation of the cervix uteri prior to surgical pregnancy termination.

3. For use in combination with a prostaglandin analogue for termination of pregnancy between 13 and 20 weeks gestation.
4. For the expulsion of a dead foetus *in utero*.

MIFEGYNE® must not be administered if there is doubt as to the existence or age of the pregnancy. The medical practitioner should in this case perform an ultrasound scan and/or measure the HCG (human chorionic gonadotropin) before administration.

4.2 Posology and method of administration

Posology

1. Medical alternative to surgical termination of intra-uterine pregnancy:

600 mg (3 x 200 mg MIFEGYNE® tablets) is taken by mouth as a single dose. Unless abortion has already been completed, a prostaglandin analogue must be administered orally, 36 to 48 hours later.

During the period immediately following the administration of the prostaglandin analogue, the patient may need medicine for cramps or gastrointestinal symptoms. The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a telephone number to call if she has questions following the administration of the prostaglandin analogue. In addition, the name and telephone number of the medical practitioner who will be handling emergencies should be provided to the patient.

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

600 mg (3 x 200 mg MIFEGYNE® tablets) followed 36 to 48 hours later by surgical termination of pregnancy.

Softening and dilation has been shown to be detectable from 24 hours after administration and increases to a maximum at approximately 36 to 48 hours after administration.

Surgery should be performed no later than 48 hours after administration of MIFEGYNE®, since when the time elapsed between MIFEGYNE® administration and surgery is more than 48 hours the

risk of bleeding and abortion prior to surgery, particularly with pregnancies of earlier gestations (less than 9 weeks), is increased.

3. For use in combination with a prostaglandin analogue for termination of pregnancy between 13 and 20 weeks gestation:

600 mg (3 x 200 mg MIFEGYNE® tablets) is taken by mouth as a single dose followed 36 to 48 hours later by a prostaglandin analogue. The prostaglandin analogue is to be repeated as many times as necessary. If abortion does not occur within 48 hours after the first prostaglandin analogue administration, an alternative procedure of uterine emptying should be followed. It is not necessary to perform a dilation and curettage procedure if it is clear that a complete abortion has occurred.

4. For the expulsion of a dead foetus *in utero*:

600 mg (3 x 200 mg MIFEGYNE® tablets) taken in a single dose for two consecutive days. Labour should be induced by the usual methods if it has not started within 72 hours following the first administration.

The dosage is independent of body weight.

Method of administration

MIFEGYNE® tablets are for oral use only.

4.3 Contraindications

MIFEGYNE® should not be used in:

- Known hypersensitivity to mifepristone or to any excipients of MIFEGYNE® listed in section 6.1.
- Chronic adrenal failure.
- Asthmatics (severe asthma uncontrolled by corticosteroid therapy) and other patients with chronic obstructive airways disease.
- Suspected ectopic pregnancy.

- Long-term corticosteroid therapy.
- Haemorrhagic disorders and treatment with anticoagulants.
- Porphyria.
- Pregnancy not confirmed by ultrasound scan or biological tests.
- Unremoved intra-uterine contraceptive device.
- Contraindication to the prostaglandin analogue selected.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering medical practitioner.

MIFEGYNE® should also not be used in patients who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Patient Information Leaflet and the Patient Agreement provided with the MIFEGYNE® carefully and should be given a copy of the product label for their review. Patients should discuss their understanding of these materials with their health care providers, and retain the present information leaflet for later reference.

4.4 Special warnings and precautions for use

Because of its abortifacient properties, mifepristone, as in MIFEGYNE®, should never be used in a woman with an ongoing pregnancy who wants to complete it.
The age of the pregnancy must be determined from the questioning and the clinical examination of the patient. Uterine ultrasound is recommended.

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see section 4.8).

In patients who experience severe cutaneous adverse reactions, treatment with MIFEGYNE® should be immediately discontinued. Retreatment with MIFEGYNE® is not recommended.

The pharmacokinetics, safety and tolerability of mifepristone 200 mg were investigated in women with moderate hepatic impairment versus healthy women participants with normal hepatic function. The results on the total plasma concentrations data concluded that no lack of efficacy or changes in the safety profile were likely. However, the possible consequences of moderate hepatic impairment on the unbound fraction could not be determined. The clinical consequences of 200 mg mifepristone administration in patient with moderate hepatic impairment are unknown.

MIFEGYNE® is not recommended in patients with:

- Malnutrition.
- Hepatic failure.
- Renal failure.

MIFEGYNE® should be used with caution in:

- Patients with cardiovascular disease or risk factors.
- Patients with prosthetic heart valves – those patients who have had one previous episode of infective endocarditis should receive chemoprophylaxis.
- Multiparous women and women with a history of caesarean section – The risk of uterine rupture may be increased in such patients.
- Smokers over 35 years of age, especially when used in combination with a prostaglandin analogue.

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 a prostaglandin analogue to be administered at a second visit 36 – 48 hours after administration of MIFEGYNE®,

- the need for a follow-up visit within 10 to 14 days after intake of MIFEGYNE® in order to check for complete expulsion,
- the possible failure of the method, which may require 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®.

Risks related to the method

Failures

The risk of failure makes the control visit mandatory in order to check that the expulsion is completed.

In cases of non-complete expulsion, a surgical revision may be necessary. The efficacy of 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 12 days or more after MIFEGYNE® intake) which may be heavy.

Bleeding occurs in almost all cases and is not in any way a proof of complete expulsion and for this reason a follow-up visit is absolutely necessary, to confirm termination of pregnancy.

The bleeding can occur very quickly after MIFEGYNE® intake, and sometimes later:

- In 60 %, expulsion occurs within 4 hours following MIFEGYNE® intake.
- In the remaining 40 % of the cases, expulsion occurs within 24 to 72 hours following MIFEGYNE® intake.

The expulsion may occur before administration of the prostaglandin analogue (in about 3 % of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

The patient should be informed not to travel far away from the health care facility 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. This is bleeding that lasts longer than 12 days and/or that is heavier than the normal menstrual bleeding.

It should be noted that in pregnancies of 8 to 9 weeks gestation, blood loss may be heavier than that seen at earlier gestations.

A follow-up visit is mandatory and must take place within a period of 10 to 14 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.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an undiagnosed ectopic pregnancy, and appropriate treatment should be considered.

Patients must be informed that in the event of the failure or interruption of the method, the pregnancy is liable to continue to develop. The foetus may be exposed to a risk of malformation. It is essential that termination of pregnancy by another method be undertaken at a follow-up visit in the event of such failure.

Bleeding may continue for 30 days or more in up to 8 % of patients. In some cases, excessive bleeding may require treatment by vasoconstrictor medicines, curettage, administration of saline

infusions, and/or blood transfusion. 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.

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.

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

Infection

Serious cases (including fatal cases) of toxic shock and septic shock following infection with atypical pathogens (*Clostridium sordellii* or *Escherichia coli*) have been reported after medical abortion with the use of MIFEGYNE® followed by unauthorised vaginal or buccal administration of misoprostol tablets.

Medical practitioners should be aware of this potentially fatal complication.

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 (see section 4.2).

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.

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 MIFEGYNE®.

Due to the antiglucocorticoid activity of mifepristone, as in MIFEGYNE®, 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.

The medical termination of pregnancy requires rhesus determination and hence the prevention of rhesus alloimmunisation as well as other general measures usually taken during any termination of pregnancy.

Patients must be informed that subsequent pregnancy may occur between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to MIFEGYNE®, it is recommended to start contraception immediately.

Uterine pain may be experienced, more often during the first few hours after administration. Analgesia may be required. Nulliparous women and those with a history of dysmenorrhoea are more likely to require narcotic analgesia.

4.5 Interaction with other medicines and other forms of interaction

A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of nonsteroidal antiinflammatory drugs (NSAIDs) including aspirin (acetylsalicylic acid). As the efficacy of treatment could be affected, the use of NSAIDs, including aspirin, should be avoided until pregnancy termination is complete. For termination of pregnancy of up to 63 days

gestation, NSAIDs should not be given at least until the follow-up visit 8 to 12 days after mifepristone administration.

Effect of other medicines on MIFEGYNE®

Concomitant administration of mifepristone with the CYP3A4 inhibitor itraconazole, increased mifepristone AUC and exposure of its metabolites 22-hydroxy mifepristone and *N*-demethyl mifepristone.

C_{max} was increased by 1,5-fold for mifepristone and 1,8-fold for 22 hydroxy mifepristone and decreased to 0,7-fold for *N*-demethyl mifepristone. Increased exposure is expected when mifepristone is given concomitantly with a strong CYP3A4 inhibitor. However, this is most likely not clinically relevant. No dose adjustment is needed when mifepristone is given concomitantly with a CYP3A4 inhibitor (e.g. itraconazole, ketoconazole, erythromycin or grapefruit juice).

Reduced efficacy can be expected when MIFEGYNE® is given concomitantly with a CYP3A4 inducer (e.g. rifampicin, dexamethasone, St John's wort and certain anticonvulsants as phenytoin, phenobarbital (phenobarbitone), carbamazepine).

In case a medical termination of developing intra-uterine pregnancy is to be done for a patient treated with a strong or moderate CYP3A4 inducer, it is advised to administer a single oral dose of 600 mg (i.e. 3 tablets of 200 mg each), followed 36 to 48 hours later by the administration of the prostaglandin analogue (see section 4.2).

Effect of mifepristone on other medicines

In vitro and *in vivo* data indicate that mifepristone is an inhibitor of CYP3A4. Coadministration of mifepristone may lead to an increase in serum levels of medicines that are metabolised by CYP3A4. Due to 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 MIFEGYNE® is administered with medicines that are CYP3A4 substrates and have narrow

therapeutic range, including some medicines used during general anaesthesia.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animals (see section 5.3), the abortifacient effect of mifepristone, as in MIFEGYNE®, precludes the proper assessment of any teratogenic effect of the molecule.

With subabortive doses, malformations were observed in rabbits, but not in rats, mice or monkeys. 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. One of the possible mechanisms might be amniotic band syndrome. 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 risk to the foetus, the follow-up visit is mandatory (see section 4.4).
- Should a failure of the method be diagnosed at the follow-up 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, a careful ultrasound monitoring of the pregnancy, with a special attention to the limbs, must be established in a specialised centre.

Breastfeeding

Mifepristone is excreted in mother's milk in small amounts. MIFEGYNE® should be avoided during breastfeeding.

Fertility

Mifepristone does not affect fertility. It is possible that the woman becomes pregnant again as soon

as the termination of pregnancy is completed. Therefore, it is important to inform the patient to start contraception immediately after the termination of the pregnancy is confirmed.

4.7 Effects on ability to drive and use machines

MIFEGYNE® may cause dizziness (see section 4.8). The patient should be advised not to drive or operate machines until the effects of MIFEGYNE® are known.

4.8 Undesirable effects

The frequencies of occurrence of side effects are classified as follows:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1 000 to < 1/100)

Rare (≥ 1/10 000 to < 1/1 000)

Very rare (< 1/10 000)

Not known (cannot be estimated from the available data)

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 and septic shock (caused by *Clostridium sordellii* or *Escherichia coli*), which can be with or without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of unauthorised vaginal or buccal administration of misoprostol tablets for oral use. Medical practitioners should be aware of this potentially fatal complication (see section 4.4).

Metabolic and nutritional disorders:

Not known: Hypoglycaemia.

Nervous system disorders:

Common: Dizziness, headache.

Vascular disorders:

Uncommon: Hypotension.

Gastrointestinal disorders:

Very common: Abdominal pain, nausea*, vomiting*, diarrhoea*, cramping (light or moderate).

Hepatobiliary disorders:

Not known: Increase in hepatic enzymes.

Skin and subcutaneous tissue disorders:

Uncommon: Hypersensitivity, skin rashes, urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis have also been reported, angioedema.

Not known: Acute generalised exanthematous pustulosis.

Renal and urinary disorders:

Not known: Increases in urea and creatine.

Reproductive system and breast disorders:

Very common: Uterine bleeding, uterine pain, contractions or cramping in the hours following prostaglandin intake. Heavy bleeding which may require haemostatic curettage.

Rare: Uterine rupture, during induction of second trimester termination of pregnancy or labour induction for foetal death in utero within the third trimester, uterine rupture has been reported less frequently after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

General disorders and administration site conditions:

Rare: Fever, malaise, vagal symptoms (hot flushes, dizziness, chills).

*These gastrointestinal effects related to prostaglandin use are frequently reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MIFEGYNE® is important. It allows continued monitoring of the benefit/risk balance of MIFEGYNE®. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No case of overdose has been reported.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.12 Hormone inhibitors.

Pharmacotherapeutic group: Other sex hormone and modulator of the reproductive function/antiprogestogen.

ATC code: GO3XB01

Mifepristone is a synthetic steroid with an anti-progestational action as a result of competition with progesterone at the progesterone receptors. In women, at doses greater than or equal to 1 mg/kg orally, mifepristone antagonises the endometrial and myometrial effects of progesterone. During

pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandins. During the first trimester, it allows the dilation and opening of the *cervix uteri*.

Mifepristone binds to the glucocorticoid receptor. It does not bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In man, the antiglucocorticoid action is observed at a dose equal to or greater than 4,5 mg/kg, which triggers a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol.

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

5.2 Pharmacokinetic properties

Absorption

After oral administration of a single dose of 600 mg the peak concentration of 1,98 mg/L is reached after 1,3 hours. The absolute bioavailability is 69 %.

Distribution

The active substance is 98 % bound to plasma proteins: albumin
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.

Biotransformation

Two primary metabolic pathways have been demonstrated: *N*-demethylation and terminal hydroxylation of the 17-propynyl chain.

Elimination

After a distribution phase, elimination is at first slow, the concentration decreasing by a half

between about 12 and 72 hours, and then more rapidly, giving an elimination half-life of 18 hours. Mifepristone is mainly excreted in faeces. After administration of a 600 mg labelled dose, 10 % of the total radioactivity is eliminated in the urine and 90 % in the faeces.

Linearity

Mifepristone shows non-linear pharmacokinetics.

Characteristics in specific groups of subjects or patients

Hepatic impairment

A study has been done on 8 women with moderate hepatic impairment versus 8 women with normal hepatic function, treated with a single oral dose of mifepristone 200 mg to assess the mifepristone and its metabolites (*N*-demethylated metabolite, hydroxylated metabolite and di-demethylated metabolite) pharmacokinetic. The total C_{max} of mifepristone and its metabolites were reduced by half in patients with moderate hepatic impairment compared to normal hepatic function participants. Similarly, the total AUC∞ was reduced by 43 % and 50 % for mifepristone and *N*-demethylated metabolite in patients with moderate hepatic impairment compared to normal hepatic function participants. This decrease in exposure could be caused by a decrease in absorption and/or protein binding. But it is clinically most likely not relevant as the assessment of mifepristone and its metabolites unbound fractions (0,2 to 6 %) could not be performed with enough accuracy to be able to discriminate any significant variation between the two groups. Considering the above, the clinical consequences of 200 mg mifepristone administration in patient with moderate hepatic impairment are unknown.

5.3 Preclinical safety data

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.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect

of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, foetal anomalies were observed (cranial vault, brain and spinal cord). The effect was dose-dependent. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment. No evidence of teratogenicity was observed in post-implantation rat and monkey embryos exposed to mifepristone *in vitro*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silica, anhydrous

Maize starch

Povidone

Microcrystalline cellulose

Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

A carton containing 3 tablets, which are packed into a thick white (polyvinyl chloride acetochloride) sheet sealed onto a thick aluminium foil printed on one side.

Pack size: 3 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Medi Challenge (Pty) Ltd

493 De Jonge Street

Elardus Park

Pretoria

0181

Tel: 011 462 5491

8. REGISTRATION NUMBER

34/21.12/0328

9. DATE OF FIRST AUTHORISATION

06 August 2001

10. DATE OF REVISION OF THE TEXT

24 July 2026