If MEDIPRIST 200 mg results in incomplete abortion, surgical intervention may be necessary. Prescribers must give patients clear instructions on the process to be followed in the event of an emergency following administration of MEDIPRIST 200 mg.

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE
MEDIPRIST 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg of mifepristone.
MEDIPRIST 200 mg is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets

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

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
- Medical termination of intra-uterine pregnancy of up to 63 days after the first day of the last menstrual period and/or ultrasound scan, in combination with a prostaglandin E1 analogue.
- Softening and dilation of the cervix uteri prior to surgical termination of pregnancy.
- For use in combination with a prostaglandin for termination of pregnancy between 13 and 20 weeks gestation.
- Labour induction after foetal death in utero, in patients where prostaglandin or oxytocin cannot be used.

MEDIPRIST 200 mg must not be administered if there is doubt as to the existence or age of the pregnancy. The prescribing doctor should in this case perform an ultrasound scan and/or measure the HCG before administration.

4.2 Posology and method of administration
1. **Medical termination of intra-uterine pregnancy up to 63 days after the last menstrual period:**

MEDIPRIST 200 mg (1 tablet) to be taken by mouth as a single dose. Unless abortion has already been completed, a suitable prostaglandin analogue should be administered 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 phone number to call if she has questions following the administration of the prostaglandin analogue. In addition, the name and phone 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 during the first trimester.

MEDIPRIST 200 mg (1 tablet) to be taken by mouth 36 to 48 hours before (but not beyond) the surgical termination of pregnancy.

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

Surgery should be performed no later than 48 hours after administration of MEDIPRIST 200 mg, since when the elapsed time between MEDIPRIST 200 mg administration and surgery is more than 48 hours the risk of bleeding and abortion 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 of mifepristone (3 x MEDIPRIST 200 mg 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. Labour induction after foetal death in utero in patients where prostaglandin or oxytocin cannot be used:

600 mg of mifepristone (3 x MEDIPRIST 200 mg tablets) taken by mouth 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.

Dose adjustment to a higher dose (600 mg) is needed with concomitant treatment with CYP3A4 inducers (see section 4.5).

4.3 Contraindications

MEDIPRIST 200 mg should never be prescribed in the following situations:

- known hypersensitivity to mifepristone or to any of the excipients of MEDIPRIST 200 mg listed in section 6.1.
- chronic adrenal failure
- asthmatics (severe asthma uncontrolled by corticosteroid therapy) and other patients with chronic obstructive airways disease
- inherited porphyria
- suspected ectopic pregnancy
- pregnancy not confirmed by an ultrasound or biological test
- pregnancy beyond 63 days of amenorrhoea
- pregnancy of 84 days of amenorrhoea and beyond (for softening and dilation of the cervix prior to surgical termination of pregnancy)
- contraindication to the prostaglandin analogue selected
- long-term corticosteroid therapy
- haemorrhagic disorders and treatment with anticoagulants
- unremoved intra-uterine contraceptive device.

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 doctor.

MEDIPRIST 200 mg also should not be used by any patient 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 provided with MEDIPRIST 200 mg. 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

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, re-treatment with mifepristone is not recommended.

The pharmacokinetics, safety and tolerability of MEDIPRIST 200 mg were investigated in women with moderate hepatic impairment versus healthy women participants with normal hepatic function. Statistical analyses of total AUC_{∞} and C_{max} for the mifepristone, N-demethylated metabolite, hydroxylated metabolite and di-demethylated metabolite showed a decrease in both overall peak and exposure in patients with moderate hepatic impairment compared to healthy-matched participants. In conclusion, the clinical consequences of 200 mg mifepristone administration in patients with moderate hepatic impairment are unknown.

MEDIPRIST 200 mg is not recommended in patients with:

- Renal failure
- Hepatic failure
- Malnutrition

Medical termination of developing intra-uterine pregnancy:

This method requires the involvement of the woman who should be informed of the requirements of the method which are:

- 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 MEDIPRIST 200 mg in order to check for complete expulsion.
- The possible risk of failure (see section 5) of the method which may require 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 MEDIPRIST 200 mg.

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.

The risks related to the method must be taken into account and explained to the patient:

- **Failures:**

The risk of failure, which occurs in up to 11,7 % of the cases, 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 the method decreases with parity and consequently increasing of age of the woman.

- **Bleeding:**

Bleeding is an almost constant part of the procedure, whatever the prostaglandin use, and at any pregnancy term although it is usually more abundant when pregnancy age increases. It can occur after MEDIPRIST 200 mg alone.

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of 10 to 16 days after MEDIPRIST 200 mg intake) which may be heavy. **Bleeding occurs in almost all cases and is not in any way proof of complete expulsion and for this reason a follow-up visit is absolutely necessary, to confirm termination of pregnancy.**

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.

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 must take place within a period of 10 to 14 days after administration of MEDIPRIST 200 mg 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.

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.

Since heavy bleeding requiring haemostatic curettage occurs in up to 5 % 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 medical practitioners according to the type of haemostatic disorder and the level of anaemia.

- **Infection:**

Cases of fatal toxic shock caused by *Clostridium sordellii* endometritis presenting with or without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone, as in MEDIPRIST 200 mg followed by non-authorised vaginal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication.

- **In all instances:**

The use of MEDIPRIST 200 mg requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually 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 MEDIPRIST 200 mg, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after MEDIPRIST 200 mg administration.

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of MEDIPRIST 200 mg.

Due to the antiglucocorticoid activity of MEDIPRIST 200 mg, 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 MEDIPRIST 200 mg. 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 MEDIPRIST 200 mg or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

MEDIPRIST 200 mg should also be used with caution in the following patients:
- Smokers over 35 years of age, especially when used in combination with a prostaglandin analogue.
- 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.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interaction

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). Some 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.

Pharmacokinetic interactions

Effect of other medicines on mifepristone

Concomitant administration of mifepristone with CYP3A4 inhibitor itraconazole increased mifepristone AUC by 2,6-fold and its metabolites 22-hydroxy mifepristone and N-demethyl mifepristone exposure by 5,1-fold and 1,5-fold, respectively. 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 (C_{max} increases 1,5-fold). 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).

Concomitant administration of mifepristone as contained in with CYP3A4 inducer rifampicin was shown to decrease mifepristone AUC by 6,3-fold and its metabolites 22-hydroxy mifepristone and N demethyl mifepristone by 20-fold and 5,9-fold, respectively. Therefore, reduced efficacy can be expected when mifepristone is given concomitantly with a CYP3A4 inducer (e.g., rifampicin, dexamethasone, St. John's Wort and certain anticonvulsants such as phenytoin, phenobarbital, carbamazepine).

Therefore, in case of a patient treated with 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 gemeprost 1 mg per vagina.

Effect of mifepristone on other medicines
In vitro and *in vivo* data indicates that mifepristone is an inhibitor of CYP3A4. Co-administration 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 mifepristone 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
MEDIPRIST 200 mg is indicated for the termination of pregnancy and has no other use during pregnancy.
- The patient should be informed that due to the risk of failure of the medical method of pregnancy termination and the unknown risk to the foetus, the control visit is mandatory (See section 4.4).
- 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 ultra-sonographic monitoring of the pregnancy will be established, with a special attention to the limbs.

Breastfeeding
It is unknown whether MEDIPRIST 200 mg is excreted in the mother's breast milk. Consequently, MEDIPRIST 200 mg use should be avoided during breastfeeding.

Fertility
Pregnancies may occur between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to MEDIPRIST 200 mg, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after MEDIPRIST 200 mg administration.

4.7 Effects on ability to drive and use machines
MEDIPRIST 200 mg may make you dizzy. Do not drive or operate machinery until you know how MEDIPRIST 200 mg affects you.

4.8 Undesirable effects
The adverse events reported with MEDIPRIST 200 mg, classified according to frequency and system organ class, are summarised below in tabular format:

MedDRA	Adverse events (frequency)		
System Organ Class	**Frequent**	**Less frequent**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Infection following abortion, suspected or confirmed infections (pelvic inflammatory disease)	Toxic shock syndrome	
Neoplasms benign and malignant (including cysts and polyps)		Elevated alpha-feto protein, elevated carcinoembryo- genic antigen	
Blood and lymphatic system disorders		Thrombotic thrombocytopenic purpura, thrombocytopenia, induced systemic lupus erythematous	
Psychiatric disorders		Mania	
Nervous system disorders	Headache, dizziness	Epilepsy, neurogenic tinnitus	
Eye disorders		Ophthalmoplegia	
Cardiac disorders		Myocardial infarction, induced Adams-Stokes syndrome	
Vascular disorders		Hot flush, superficial thrombophlebitis, hypotension	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, induced bronchial asthma	
Gastrointestinal disorders	Nausea, vomiting diarrhoea, gastric discomfort, abdominal pain, cramping (can be light or moderate)	Gastric bleeding	
Hepato-biliary 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*	Acute generalised exanthematous pustulosis

Musculoskeletal and connective tissue disorders		Limb spasm	
Renal and urinary disorders		Renal failure	
Pregnancy, puerperium and perinatal conditions	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 tumour, 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, fainting	Anaphylaxis, periorbital oedema, malaise, vagal symptoms	

* Including occasional case reports

Bleeding is an almost constant part of the procedure, whatever the prostaglandin use, and at any pregnancy term although it is usually more abundant when pregnancy age increases. It can occur after mifepristone alone. When heavy, it often reflects incomplete abortion leading to a surgical procedure in approximately 5 percent of the cases. It can necessitate a blood transfusion in 0,5 to 1 percent of the cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Reporting can also be done directly to Adcock Ingram Limited at:

Adcock Ingram Limited:

E-mail: Adcock.aereports@adcock.com

Tel: 011 635 0134

4.9 Overdose
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.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 21.12 Hormone inhibitor.
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 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.

During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the *cervix uteri*.

Mifepristone binds to the glucocorticoid receptor. It does not bind to mineralocorticoid receptors. A predominant effect in humans at a dose equal to or greater than 4,5 mg/kg is blockade of the feedback inhibition by cortisol of Adrenocorticotropic hormone (ACTH) secretion from the pituitary, thus increasing both corticotrophin and adrenal steroid levels in plasma.

5.2 Pharmacokinetic properties
After oral administration of a single dose of 200 mg mifepristone the peak concentration of 2,7 mg/l is reached after 0,75 hours (mean of 49 subjects). The half-life of mifepristone is 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.

The absolute bioavailability of oral mifepristone is 69 %.

In plasma mifepristone is 98 % bound to plasma proteins: mainly to albumin and alpha-1-acid glycoprotein.

N-mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4. The metabolites are excreted in the bile and eliminated in the faeces. Only a small fraction is detected in the urine.

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.

Considering the above, the clinical consequences of 200 mg mifepristone administration in patient with moderate hepatic impairment are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Magnesium stearate
Maize starch
Povidone
Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Transparent, colourless PVC-PVDC/ Aluminium blister of 1 tablet.
Pack sizes with 1 tablet and 30 tablets (as hospital pack) are provided in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER

47/21.12/0034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 March 2019

10. DATE OF REVISION OF THE TEXT

30 September 2024