**SCHEDULING STATUS: S4**

## 1. NAME OF MEDICINE

ACEMIFE 200 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACEMIFE: Each tablet contains 200 mg mifepristone

Sugar free

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

ACEMIFE: light yellow coloured, round shaped, uncoated tablets with break line on one side and plain on the other side

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ACEMIFE is indicated for

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.

ACEMIFE 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

Posology

Medical alternative to surgical termination of intrauterine pregnancy:

600 mg mifepristone (3 x 200 mg ACEMIFE 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 medication 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.

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

600 mg (3 x 200 mg ACEMIFE 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 ACEMIFE, since when the time elapsed between ACEMIFE 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.

For use in combination with a prostaglandin analogue for termination of pregnancy·

600 mg of mifepristone (3 x 200 mg ACEMIFE 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.

For the expulsion of a dead foetus in utero.

600 mg (3 x 200 mg ACEMIFE 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

For oral use

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

ACEMIFE should not be used:

- Patients with renal failure.
- Asthmatics (severe asthma uncontrolled by corticosteroid therapy) and other patients with chronic obstructive disease.
- Suspected ectopic pregnancy.
- Long-term corticosteroid therapy.
- Haemorrhagic disorders and treatment with anticoagulants.
- Porphyria.
- Unremoved intra-uterine contraceptive device.
- Pregnancy not confirmed by ultrasound scan or biological tests

Because it is Important to have access to appropriate medical care if an emergency develops, the treatment procedure is contra-indicated 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.

ACEMIFE 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.

### 4.4 Special warnings and precautions for use

ACEMIFE should be used with caution in the following patients:

• Patients with cardiovascular disease or risk factors.

• Patients with hepatic failure.

• 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.

The patient must be informed that vaginal bleeding occurs in almost all cases. This is not in any way a proof of complete expulsion and that for this reason a follow-up visit is absolutely necessary, to confirm termination of pregnancy. ·

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 hypercoagulability, or severe anaemia.

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

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 mifepristone 200 mg followed by unauthorised vaginal or buccal administration of misoprostol tablets. Clinicians should be aware of this potentially fatal complication.

**A follow-up visit is mandatory and must take place within a period of 10 to 14 days after administration of *[PRODUCT NAME]* to verify by the appropriate means {clinical examination, ultrasound scan, etc.) that expulsion has been completed and that vaginal bleeding has stopped (apart from light bleeding which should disappear within a few days).**
**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.**

Patients must be informed that subsequent pregnancy may occur without intervening menstruation and that contraception should be used.

### 4.5 Interaction with other medicines and other forms of interaction

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.

No interaction studies have been performed. On the basis of this medicine'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).

## 4.6 Fertility, pregnancy and lactation

Pregnancy:

This product is indicated for the termination of pregnancy and has no other use during pregnancy.

Breastfeeding:

It is unknown whether this product is distributed into breast milk. ACEMIFE 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

No data showing an effect on the ability to drive or using machines are known. Dizziness could occur as a side effect inherent of the abortion process. When driving or using machines one should take this possible side effect into account.

## 4.8 Undesirable effects

**Infections and Infestations:**

Frequent: endometritis, pelvic inflammatory disease

Frequency unknown: Bacterial infection (systemic), septic shock

**Metabolic and nutritional disorders:**

Frequency unknown: Hypoglycaemia

**Nervous system disorders:**

Frequent: Dizziness

Less frequent: headache

**Vascular disorders:**

Less frequent: Hypotension

**Gastrointestinal disorders:**

Frequent: Abdominal pain, nausea, vomiting, diarrhoea, light or moderate cramping

**Hepato-biliary disorders:**

Frequency unknown: Increase in hepatic enzymes

**Skin and subcutaneous tissue disorders:**

Less frequent: Skin rash, urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis, angioderma

**Renal and urinary disorders:**

Frequency unknown: Increases in urea and creatine

**Reproductive system and breast disorders:**

Frequent: Uterine bleeding, uterine pain or cramping

Less frequent: Uterine rupture

**Other:**

Less frequent: Fever, chills

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 Overdose**

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8)

Treatment is supportive and symptomatic.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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 antlglucocorticoid action is observed at a dose equal to or greater than 4.5mglkg which triggers a compensatory elevation of 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

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% and the active substance is 98% bound to plasma proteins.

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.

Two primary metabolic pathways (of hepatic oxidative metabolism) have been demonstrated: N-demethylation and terminal hydroxylation of the 17-propynyl chain.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose

Maize starch

Povidone (K30)

Sodium lauryl sulphate

Croscarmellose sodium

Colloidal silicon dioxide

Magnesium stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Store at or below 25°C.

Store in the original package.

Keep out of reach of children.

### 6.5 Nature and contents of container

ACEMIFE is packed in blister pack comprising of transparent PVC/PVDC film backed by ALU foil in cartons of 1, 3, 6, 15 or 30 tablets**.**

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal of a used medicine

No special requirements.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

P.O. Box 431

Pinetown 3600

## 8 REGISTRATION NUMBER(S)

55/21.12/0761.760

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10 DATE OF REVISION OF THE TEXT