SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Brand Name **:** MARISAFE

Generic Name **:** Mifepristone Tablet 200 mg and Misoprostol Tablets 200 mcg in a combipack.

2. QUALITATIVE AND QUANTITATIVE

COMPOSITIONLabel Claim for Mifepristone tablet

Each uncoated tablet contains:

Mifepristone 200 mg

Excipients..... q.s.

Label Claim for Misoprostol tablet

Each uncoated tablet contains:

Misoprostol……200 mcg

Excipients..... q.s.

3. PHARMACEUTICAL FORM

Light yellow round, biconvex tablets debossed with “J09” on one side and plain on the other side one tablet of mifepristone 200 mg pack in a blister

White to off-white, round, bevel edged, flat faced tablets with “J” debossed above and “08” below the score line on one side and plain on other side. 4 tablets of misoprostol 200 mcg pack in a blister

4. Clinical particulars

Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack can only be prescribed and administered in accordance with the countries national laws and regulations.

4.1 Therapeutic indications

Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack is indicated for medical termination of developing intra-uterine pregnancy of up to 63 days of amenorrhea.

4.2 Posology and method of administration

Posology

200mg of mifepristone (one tablet) is taken in a single oral dose, followed 36 to 48 hours later, by the administration of misoprostol 800 micrograms (i.e. 4 tablets of 0.2mg each) vaginally or orally (Depending upon preference and amount of bleeding). If the patient vomits shortly after administration of mifepristone, she should inform the doctor.

Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack has only been studied in women over age 18.

Pediatric population

The Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack t is not evaluated for use in children and adolescents.

Method of administration

Misoprostol tablets can be administered by a health care provider (place two tablets on each side of the cervix in vaginal vault) or by the woman herself. The woman should be instructed to clean her hands thoroughly before inserting the misoprostol tablets as high as possible into the vagina, and remain recumbent for at least 30 minutes

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4.3 Contraindications

This Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack should never be prescribed in the following situations:

- Pregnancy not confirmed by gynaecological examination, ultrasound scan or biological tests,
- Pregnancy beyond 63 days of amenorrhoea,
- confirmed or suspected extra-uterine pregnancy,
- Previous known allergy to prostaglandins,
- Severe asthma uncontrolled by therapy,
- inherited porphyria,
- Chronic adrenal failure,
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

In the absence of specific studies, caution is advised when Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack use is considered in patients with:

- Renal failure
- Hepatic failure
- Malnutrition.

Patients with prosthetic heart valves or who have had one previous episode of infective endocarditis should receive appropriate prophylactic antibiotic treatment.

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

- The necessity to take the two drugs sequentially, i.e. to first take mifepristone and then follow with misoprostol to be administered 36-48 hours later,
- The need for a follow-up visit within 14-21 days after intake of mifepristone in order to check that abortion is complete,
- The possibility of failure of the method which may require pregnancy termination by a surgical method.

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

The expulsion of the Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack of conception may take place before misoprostol administration (in 1 to 2% of cases). This does not preclude the follow-up visit in order to check that abortion is complete.

Before Mifepristone 200 mg tablets and Misoprostol 200 mcg tablets in a combipack is given to a woman who has undergone genital mutilation (FGM) a physical examination must be performed by a qualified trained medical professional to exclude any anatomical obstacles to medical abortion.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure should only be performed where the patient has access to medical facilities equipped to provide surgical treatment for incomplete abortion, or emergency blood transfusion or resuscitation during the period from the first visit until discharged by the administering qualified medical professional.

• Risks related to the method

- Failures

The non-negligible risk of failure, which occurs in 4.5 to 7.8% of the cases, makes the follow-up visit mandatory in order to check that abortion is complete.

The patient should be informed that surgical treatment may be required to achieve complete abortion.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 13 days after mifepristone intake, up to three weeks in some women). In a few cases, heavy bleeding may require surgical evacuation of the uterus. Bleeding is not in any way a proof of termination of pregnancy as it occurs also in most cases of failure. The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been confirmed. She should receive precise instructions as to whom she should contact and where to go, in the event of any problems or emergency, particularly in the case of very heavy vaginal bleeding. A follow-up visit must take place within a period of 14-21 days after administration of mifepristone to verify by the appropriate means (clinical examination, ultrasound scan, or beta-hCG measurement) that expulsion the abortion has been completed and that vaginal bleeding has stopped or substantially reduced. In case of persistent bleeding (even light) beyond the follow-up visit, its disappearance should be checked a few weeks later. 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 investigation/treatment should be considered. In the event of an ongoing pregnancy diagnosed at the follow-up visit, termination by another method should be proposed to the woman. Since heavy bleeding requiring hemostatic curettage occurs in 0.2 to 1.8% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemostatic disorders with hypercoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialized consultants according to the type of hemostatic disorder and the level of anemia.

-Infection

The genital tract is more susceptible to ascending infection when the cervix is dilated after abortion or childbirth. There are few data on the incidence of clinically significant pelvic infection after medical abortion, but it seems to be rare and probably occurs less often than after vacuum aspiration. Many of the symptoms of pelvic infection, such as pain, are often non-specific and hence precise diagnosis is difficult. In women with clinical signs such as pelvic pain, abdominal or adnexal tenderness, vaginal discharge and fever, a pelvic infection should be suspected and appropriate treatment should be given.

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 200mg mifepristone followed by non-authorized vaginal administration of misoprostol tablets for oral use. It cannot be excluded that this infection may occur also with vaginal misoprostol as in Product Clinicians should be aware of this potentially fatal complication.

•Other risks

Pregnancy-related symptoms such as nausea and vomiting may increase after mifepristone and increase further after misoprostol administration, and they will weaken and disappear during the abortion process. Lower abdominal pain and cramping are the most common symptoms and they are related to misoprostol administration and the abortion process. If pain persists after expulsion of the products of conception, its origin should be investigated. Diarrhea is the most common

dose-related side-effect related to misoprostol use which normally does not require treatment. Some women also report chills, shivering and/or temperature rise after misoprostol administration.

Regarding rhesus determination and prevention of rhesus allo-immunisation, the same general measures apply to the use of medical abortion as during any termination of pregnancy.

Any reproductive tract infections should be treated before the medical abortion regimen is administered.

During clinical trials, pregnancies have occurred between abortion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that unprotected sexual intercourse be avoided until the appearance of the first menses after the abortion. Reliable contraceptive methods should therefore be started as early as possible after misoprostol administration.

Precautions for use

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1mg of dexamethasone antagonises a dose of 400mg 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 mifepristone. 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 misoprostol administration does not adversely influence the effects of mifepristone or misoprostol and does not reduce the clinical efficacy of medical termination of pregnancy.

Rare but serious cardiovascular accidents have been reported following the intramuscular 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 misoprostol administration

During intake and for three hours following the intake, the patient should be monitored in the treatment center, in order not to miss possible acute effects of misoprostol administration.

On discharge from the treatment center the woman 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 center by telephone or local access.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in view of the single dose administration. 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, and carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro 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 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, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine, or some agents used during general anesthesia. Antacids containing magnesium may worsen misoprostol induced diarrhea.

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

Animal studies have not evidenced teratogenicity of misoprostol but have shown its foetotoxicity at high doses.

There is currently no relevant clinical data that suggest the possible occurrence of malformation after the vaginal use of misoprostol during pregnancy. However, in a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of fetus movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and due to the unknown risk to the fetus, the follow-up visit is mandatory (see section 4.4 Special warnings and 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 are too limited to justify a systematic termination of an exposed pregnancy In that event, a careful ultrasonographic monitoring of the pregnancy should be carried out.

Lactation

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

4.7 Effects on ability to drive and use machines

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

Mifepristone and misoprostol may cause dizziness, which could have an effect on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are ranked under headings of frequency. Within each frequency grouping, the effects are presented in order of decreasing seriousness.

Very common (≥1/10)

Common (≥1/100, <1/10)

Uncommon (≥1/1,000, ≤1/100)

Rare (≥1/10,000 ≤1/1,000)

Very rare (<1/10,000), not known (cannot be estimated from the available data).

Vascular Disorders	
Rare:	Hypotension.
Gastrointestinal System	
Common:	• Cramping, light or moderate. • Nausea, vomiting, diarrhoea (these gastrointestinal effects are related to misoprostol use).
Skin and subcutaneous tissue disorders	
Uncommon:	Hypersensitivity: skin rashes.
Rare:	Urticaria, erythroderma, erythema nodosum, epidermal necrolysis.
Reproductive system and breast disorders	
Very common:	Uterine contractions or cramping (up to 70 to 80%) in the hours following misoprostol intake.
Common:	Heavy bleeding occurs in up to 5% of the cases and may require haemostatic curettage and blood transfusion in up to 1.8% of the cases.
Uncommon:	Infection following abortion: Suspected or confirmed infections (endometritis, pelvic inflammatory disease) have been reported in less than 1% of women.
General disorders and administration site conditions	
Rare:	Headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

Very rare cases of fatal toxic shock caused by Clostridium sordellii endometritis, presenting without fever or other obvious symptoms of infection, have been reported. Clinicians should be aware of this potentially fatal complication (see section 4.4. Special warnings and precautions for use).

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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The European Medicines Agency has waived the obligation to submit the results of studies with Product in all subsets of the pediatric population in medical abortion. (See section 4.2 for information on pediatric use).

Mifepristone

Other sex hormone and modulator of the genital system / antiprogestogens: G03XB01.

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

At doses ranging from 3 to 10mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonizes the endometrial and myometrial effects of progesterone. During pregnancy it sensitizes the myometrium to the contraction inducing action of prostaglandins. The maximum effect is achieved when prostaglandin was administered 36 to 48 hours after mifepristone.

Mifepristone induces softening and dilatation of the cervix, softening and dilatation has been shown to be detectable from 24 hours after administration of mifepristone and increases to a maximum at approximately 36 - 48 hours after administration.

Mifepristone binds to the glucocorticoid receptor. In animals at doses of 10 to 25mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5mg/kg by a compensatory elevation of ACTH and cortisol. Glucocorticoid bioactivity (GBA) may be depressed for several days following a single administration of 200mg mifepristone for termination of pregnancy. The clinical implications of this are unclear, however vomiting and nausea may be increased in susceptible women.

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

Misoprostol

Oxytocics / Prostaglandins: G02AD06.

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of the product of conception.

When administered vaginally, the increase in uterine tonus begins after about 20 minutes and reaches its maximum after 46 minutes. Uterine contractility increases continuously for four hours after vaginal administration. Vaginal administration of misoprostol induces far more powerful and regular contractions than does oral administration.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to the expulsion of the conceptus. In clinical trials, the success rate is around 95% when 200mg mifepristone is combined with misoprostol 800 micrograms vaginally up to 63 days of amenorrhea.

The table shows the outcome of treatment with regard to complete abortion, incomplete/missed abortion and continuing pregnancy by duration of amenorrhea from the pivotal study performed by the WHO.

Days of amenorrhea	Complete abortion		Incomplete abortion		Missed abortion		Continuing pregnancy		Undetermined outcome	
	N	%	N	%	N	%	N	%	N	%
<49	214	95.5	5	2.2	0	0	2	0.9	3	1.3

50-57	227	93.0	11	4.5	0	0	0	0	6	2.5
>57-<63	249	92.2	15	5.6	0	0	0	0	6	2.5

5.2 Pharmacokinetic properties

Mifepristone

Absorption

After oral administration of a single dose of 600mg mifepristone is rapidly absorbed. The peak concentration of 1.98mg/L is reached after 1.30 hours (means of 10 subjects).

Distribution

There is a non-linear dose response with doses of 100mg and beyond. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radioreceptorassay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

Biotransformation

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

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, 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.

Elimination

Mifepristone is mainly excreted in faeces. After administration of a 600mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

Misoprostol

Absorption

On vaginal administration, the plasma concentrations of misoprostol acid (i.e., its pharmacologically active metabolite) peak in 1 - 2 hours and then decline slowly, resulting in the sustained plasma levels up to 4 hours.

The liver is the primary site of metabolism and less than 1% of misoprostol acid is excreted in the urine.

The rate and extent of absorption of the misoprostol tablets in the Product formulation is approximately 70% higher when compared with Cytotec®, a marketed misoprostol formulation.

Elimination

The metabolites of misoprostol acid are inactive and the majority of the dose is excreted as metabolites to misoprostol and misoprostol acid in the urine.

The serum protein binding of misoprostol acid is approximately 90% and is concentration independent at therapeutic doses.

5.3 Preclinical safety data

Mifepristone

Mifepristone is shown to have no mutagenic potential and no toxic effect up to 1000mg/kg in acute administration performed in mice and rats.

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, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

Misoprostol

Single dose toxicity studies in rodents and non-rodents indicate a safety margin of at least 500 to 1000-fold between lethal doses in animals and therapeutic doses in humans. Reproductive toxicity studies in animals have shown embryotoxicity at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mifepristone tablet:

Silica colloidal anhydrous

Maize starch

Microcrystalline cellulose (PH101)

Povidone

Magnesium stearate

Purified water

Misoprostol tablet:

Microcrystalline Cellulose (Avicel PH112)

Microcrystalline Cellulose (Avicel PH113)

Sodium Starch Glycolate (Type A)

Hydrogenated Castor Oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special Precaution for Storage

Store below 30°C, Keep away from direct sunlight

Keep out of reach of children

6.5 Nature and contents of container

One tablet of Mifepristone 200 mg and four tablets of Misoprostol 200 mcg packed as Aluminum / Aluminum (cold form) blister along with pack insert in a carton.

6.6 Special precautions for disposal and other handling

No Special Requirements.

7. MANFACTURER OF PRODUCT

NAARI PHARMA PRIVATE LIMITED, INDIA

8. MARKETING AUTHORISATION NUMBER(S)

Not Applicable.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

January 2021