Summary of Product Characteristics:

1.Name of the Finished Pharmaceutical product
MARIPRIST
Combipack of Mifepristone Tablets 200 mg and Misoprostol Tablets 200 mcg

2. Qualitative and Quantitative Composition
Composition:
Each combipack contains:
1 Tablet of Mifepristone (A) and
4 Tablets of Misoprostol (B)

A) Each uncoated tablet contains:
   Mifepristone IH……200 mg
B) Each uncoated tablet contains:
   Misoprostol IH…….200 mcg
   Excipients…….q.s.

3. PHARMACEUTICAL FORM
Mifepristone Tablet for oral use
Description: Light yellow coloured, round shaped, uncoated tablets with break line on one side and plain on other side.
Misoprostol Tablets for oral use
Description: White to off white, caplet shaped, uncoated tablets, plain on both sides.

4. Clinical Particulars
4.1 Therapeutic indications
Combipack of Mifepristone 200 mg tablet and Misoprostol 200 mcg tablets is indicated for early medical abortion up to 9 weeks (63 days) of gestation.

4.2 Posology and method of administration
Posology
Mariprist is indicated for the medical termination of intrauterine pregnancy up to 63 days of gestation. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 days cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.
Any intrauterine device ("IUD") should be removed before treatment with mifepristone and misoprostol begins. Pregnancy termination by surgery is recommended in cases when **Mariprist** fails to cause termination of intrauterine pregnancy.
Mifepristone may be administered by or under the supervision of a gynecologist, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. The gynecologist must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure the patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

The dosage is mifepristone 200 mg orally followed 1-3 days later by misoprostol 800 mcg (4 tablets of 200 mcg) vaginally. The misoprostol may be administered by a clinician or self-administered by the woman. For women at 49-63 days of gestation, if abortion has not occurred 4 hours after administration of misoprostol, a second dose of misoprostol 400 mcg (2 tablets of 200 mcg) may be administered vaginally or orally (depending upon preference and amount of bleeding).

The patient should return for a follow-up visit approximately 14 days after the administration of mifepristone. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

Patients who have an ongoing pregnancy at this visit have a risk of foetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures.

Method of administration

The dosage is Mifepristone 200 mg orally followed 1-3 days later by Misoprostol 800 mcg (4 tablets of 200 mcg) vaginally.

4.3 Contraindications

Administration of mifepristone and misoprostol for the termination of pregnancy is contraindicated in patients with anyone of the following conditions:

- History of allergy or known hypersensitivity to mifepristone, misoprostol or other prostaglandin.
- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy).
- IUD in place.
- Chronic adrenal failure.
- Haemorrhagic disorders or concurrent anticoagulant therapy.
- Inherited porphyries.
- 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 physician.

4.4 Special warnings and Special precautions for use

General

The patient should not give **Mariprist** to anyone else. **Mariprist** has been prescribed for the patient's specific condition; it may not be the correct treatment for another person, and may be dangerous to the other person if she is or were to become pregnant.

Any intrauterine device ["IUD"] should be removed before treatment with mifepristone begins. Pregnancy termination by surgery is recommended in cases when **Mariprist** fails to cause termination of intrauterine pregnancy. Patients who have an ongoing pregnancy at last visit have

a risk of foetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures.

Mifepristone

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease, insulin-dependent diabetes mellitus, severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone. Although there is no clinical evidence, the effectiveness of mifepristone may be lower if misoprostol is administered more than two days after mifepristone administration.

Bleeding:

Vaginal bleeding occurs in almost all patients during the treatment procedure. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased. Normally it lasts for an average of 9 to 16 days. In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and requires prompt and immediate medical attention.

Confirmation of Pregnancy Termination:

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

Infections and Sepsis:

Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported. No causal relationship between these events and use of mifepristone and misoprostol has been established. A sustained fever of 100.4^0F or higher, severe abdominal pain, or pelvic tenderness in the days after medical abortion may indicate infection. Atypical presentation of serious infection and sepsis without these symptoms but with significant leucocytosis, tachycardia or haemoconcentration can occur.

Ectopic pregnancy:

Mifepristone is contraindicated in confirmed or suspected ectopic pregnancy since it is not effective for terminating these pregnancies. There could be a possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy since some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed mifepristone.

Misoprostol

- Some authors suggest moistening misoprostol with 3-4 drops of saline/distilled water when used for vaginal administration.

- During the period immediately following the administration of misoprostol, 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 misoprostol.

4.5 Interaction with other medicinal products and other forms of interaction.

Mifepristone:

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St.John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may indu0e mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 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 CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

Misoprostol

Misoprostol has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Misoprostol does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Misoprostol has no clinically significant effect on the kinetics of diclofenac or ibuprofen. The most common side effects of misoprostol are diarrhoea and abdominal pain. These side effects may be increased if misoprostol is taken concurrently with antacids.

Renal impairment

Misoprostol

Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max} and AUC compared to normal, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Hepatic impairment

Misoprostol

Patients with hepatic disease should receive a decreased dose.

4.6 Pregnancy and lactation

Mifepristone is indicated for use in the termination of pregnancy (through 63 days pregnancy) and has no other approved indication for use during pregnancy. Patients who have an ongoing pregnancy at the last visit have a risk of foetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures.

Teratogenic Effects

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Lactation

Mifepristone

It is not known whether mifepristone is excreted in human milk or not. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their doctor to decide if they should discard their breast milk for a few days following administration of the medications.

Misoprostol

Although it is not known whether misoprostol or misoprostol acid is excreted in human milk, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause diarrhoea in nursing infants.

4.7 Effects on ability to drive and use machines

Atenolol has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Mifepristone

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive mifepristone and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Women typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhoea. Pelvic pain, fainting, headache, dizziness and asthenia occurred rarely. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35%. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively. So by day 14, reports were rare except for reports of bleeding and spotting. Serious bacterial infection, bleeding, ectopic pregnancies that have ruptured, and death, including another death from sepsis were reported.

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 loxic 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.

Misoprostol

- Gastro-intestinal side effects like diarrhoea, abdominal pain, nausea, flatulence.
- dyspepsia, headache, vomiting and constipation.
- Shivering.
- Hyperthermia.
- Dizziness.
- Pain due to uterine contractions.
- Severe genital bleeding.
- Shock.
- Pelvic pain.
- Uterine rupture (requiring surgical repair, hysterectomy).

Incidence greater than 1%

In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving misoprostol and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%), However, there were no significant differences between the incidences of these events for misoprostol and placebo.

Causal relationship unknown:

The following adverse events were infrequently reported. Causal relationships between misoprostol and these events have not been established but cannot be executed:
Body as a whole: aches/pains, asthenia, fatigue, fever, rigors, and weight changes.
Skin: rash, dermatitis, alopecia, pallor, breast pain.
Special senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.
Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.
Cardiovascular: chest pain, oedema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.
Gastrointestinal: GI bleeding, GI inflammationlinfection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.
Hypersensitivity: anaphylaxis.
Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.
Genitourinary: polyuria, dysuria, haematuria, urinary tract infection.
Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst. impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.
Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.
Blood/Coagulation: anaemia, abnormal differential, thrombocytopaenia, purpura, ESR increased.

During Misoprostol use in Obstetrics and Gynaecology use patient may experience pain due to uterine contractions, there may be severe genital bleeding that may lead to shock. The patient can complain of Pelvic pain. There is a possibility of even uterine rupture which might require surgical repair, hysterectomy, and/or salpingo-oophorectomy.

4.9 Overdose

Mifepristone

No serious adverse reactions were reported in tolerance studies in healthy no pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold of 600mg for termination of pregnancy If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure. The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg.

Misoprostol

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy. It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for over dosage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mifepristone:

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several

animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone and the termination of pregnancy results. Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins. Mifepristone also exhibits antiglucocorticoid and weak anti-androgenic activity. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Misoprostol:

Prostaglandin E1 causes myometrial contractions by interacting with specific receptors on myometrial cells. This interaction results in a change in calcium concentration, thereby initiating muscle contraction. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract, resulting in the expulsion of the uterine contents.

5.2 Pharmacokinetic properties

Mifepristone

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution:

Mifepristone is 98% bound to plasma proteins, albumin and alpha 1-acid glycoprotein. Binding to the latter protein is saturable and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism:

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. In vitro studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, most widely found in plasma, is the N-monodemethylated metabolite, (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion:

By 11days after a 600 mg dose of titrated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11days.

Misoprostol

Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs. The compound is a lipophilic methyl ester pro-drug and is readily metabolized to the free acid, which is the biologically active

form. Following oral administration, the plasma misoprostol levels increased rapidly with a peak at 30 minutes, declined rapidly by 120 minutes, and remained low thereafter.
In contrast, after vaginal administration, the plasma concentration gradually increased, reaching maximum levels after 70-80 minutes and slowly declined with detectable levels present after 6 hours. Vaginal misoprostol was present in the circulation longer than oral misoprostol and hence its duration of stimulation of the uterus exceeds that of oral misoprostol.
Vaginal application of misoprostol results in slower increases and lower peak plasma concentrations of misoprostol acid than does oral administration, but overall exposure to the drug is increased.

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 atiandrogenic) 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 Tablets 200 mg: Microcrystalline Cellulose, Maize Starch, Povidone, Sodium Lauryl Sulphate, Croscarmellose Sodium, Colloidal Anhydrous Silica, Magnesium Stearate
Misoprostol Tablets 200 mcg: Microcrystalline Cellulose, Sodium Starch Glycolate, Hydrogenated Castor Oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C (86°F)
Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

MARIPRIST is available as:

Mono Carton: 1 Combipack of 1 tablet of Mifepristone + 4 tablets of Misoprostol in Alu-Alu pack.

Outer Carton: 10 Combipacks of 1 tablet of Mifepristone + 4 tablets of Misoprostol

6.6 Instructions for use and handling

Not Applicable

7. MARKETING AUTHORISATION HOLDER

8. NUMBER(S) IN THE NATIONAL REGISTER OF FIISHED PHARMACEUTICAL PRODUCTS

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

September 2023