

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Mifepristone Linepharma 200 mg tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of mifepristone.

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Tablet.

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

### 4. CLINICAL PARTICULARS

For termination of pregnancy, Mifepristone Linepharma 200 mg tablet and prostaglandins can only be prescribed and administered in accordance with countries national laws and regulations.
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#### 4.1 Therapeutic indications

Medical termination of a developing intra-uterine pregnancy in sequential combination with a prostaglandin analogue up to 63 days of amenorrhea.

#### 4.2 Posology and method of administration

Medical termination of developing intra-uterine pregnancy up to 63 days of amenorrhea. The method of administration is 200 mg of mifepristone in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.

Dose adjustment to a higher dose (600 mg) is needed with concomitant treatment with CYP3A4 inducers (see section 4.5 Interaction with other medicinal products and other forms of interactions).

#### *Paediatric population*

No data are available for women under 18 years.

#### 4.3 Contraindications

This product should never be prescribed in the following situations:

- known hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- chronic adrenal failure;
- asthma uncontrolled by therapy
- inherited porphyria
- pregnancy not confirmed by an ultrasound or biological test;
- pregnancy beyond 63 days of amenorrhea;
- suspected ectopic pregnancy;
- contraindication to the prostaglandin analogue selected.

#### 4.4 Special warnings and precautions for use

- *Warnings:*

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 Mifepristone Linepharma 200 mg were investigated in women with moderate hepatic impairment versus healthy women participants with normal hepatic function. Statistical analyses of total AUC $\infty$  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. This decrease in exposure could be caused by a decrease in absorption and/or protein binding. However, the possible consequences of moderate hepatic impairment on the unbound fraction could not be determined. In conclusion, the clinical consequences of 200 mg mifepristone administration in patient with moderate hepatic impairment are unknown.

In the absence of specific studies, Mifepristone Linepharma 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:

- The necessity to combine treatment with prostaglandin to be administered at a second visit.
- The need for a follow up visit (3<sup>rd</sup> visit) within 14 to 21 days after intake of Mifepristone Linepharma in order to check for complete expulsion.
- The non-negligible risk of failure (see section 5.1) 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 Mifepristone Linepharma.

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 woman:

- Failures

The non-negligible risk of failure, which occurs in up to 7.6% of the cases, makes the control visit mandatory in order to check that the expulsion is completed.

In rare case of non-complete expulsion, a surgical revision may be necessary.

The efficacy of the 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 10 to 16 days after Mifepristone Linepharma intake) which may be heavy. Bleeding occurs in almost all cases and is not in any way proof of complete expulsion. (see section 4.8).

The patient should be informed not to travel far away from the prescribing center 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.

A follow-up visit must take place within a period of 14 to 21 days after administration of mifepristone 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.

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

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 consultants according to the type of haemostatic disorder and the level of anaemia.

- Infection

Very rare cases of fatal toxic shock caused by *Clostridium sordellii* endometritis presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone 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 Mifepristone Linepharma requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg 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 Linepharma. 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 mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

The precautions related to the prostaglandin use should be noted as follows:

Rare but serious cardiovascular accidents have been reported following the use of prostaglandin analogue. For this reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Method of prostaglandin administration

During intake and for three hours following the intake, the patient should be monitored in the treatment centre, in order not to miss possible acute effects of prostaglandin administration. The treatment centre must be equipped with adequate medical facilities.

On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counseled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access.

#### **4.5 Interaction with other medicinal products 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 medicinal products 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<sub>max</sub> 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<sub>max</sub> 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 with CYP3A4 inducer rifampicin was shown to decreased 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 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 vaginam.

Effect of mifepristone on other medicinal products

*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 drugs 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 drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

#### **4.6 Fertility, pregnancy and lactation**

##### **Pregnancy**

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

With sub abortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were 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 is too limited to determine whether the molecule is a human teratogen (see section 4.8).

Consequently:

- Patient should be informed that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, 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, careful ultra-sonographic monitoring of the pregnancy should be carried out.

##### **Breast feeding**

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, limited data is available. Consequently, Mifepristone Linepharma use should be avoided during breast-feeding.

##### **Fertility**

Mifepristone inhibited oestrus cycling in rats at doses below the clinical dose in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

No human data on the effect of active substance mifepristone on fertility are available.

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

The adverse events reported with mifepristone, classified according to frequency and system organ class, are summarized in the following table:

<b>MedDRA</b>	<b>Adverse events (frequency)</b>				
<b>System Organ Class</b>	<b>Very common ≥ 1/10</b>	<b>Common ≥ 1/100 to &lt; 1/10</b>	<b>Uncommon ≥ 1/1000 to &lt; 1/100</b>	<b>Rare ≥ 1/10000 to &lt; 1/1000 and very rare (&lt; 1/10000)*</b>	<b>Not known (cannot be estimated from the available data)</b>
<b>Infections and infestations</b>			Infection	Toxic shock syndrome	
<b>Neoplasms benign, malignant and unspecified</b>				Elevated alpha-feto protein Elevated carcinoembryogenic antigen	
<b>Blood and lymphatic system disorders</b>				Thrombotic thrombocytopenic purpura Thrombocytopenia Induced systemic lupus erythematosus	
<b>Psychiatric disorders</b>				Mania	
<b>Nervous system disorders</b>	Headache			Epilepsy Neurogenic tinnitus	
<b>Eye disorders</b>				Ophthalmoplegia	
<b>Cardiac disorders</b>				Myocardial infarction Induced Adam-Stokes syndrome	
<b>Vascular disorders</b>			Hot flush Hypotension (0.25%)	Superficial thrombophlebitis	
<b>Respiratory, thoracic and mediastinal disorders</b>				Bronchospasm Induced bronchial asthma	
<b>Gastrointestinal disorders</b>	Nausea Vomiting Diarrhea Gastric discomfort Abdominal pain	Cramping, light or moderate		Gastric bleeding	
<b>Hepatobiliary disorders</b>				Abnormal liver function tests Hepatic failure Hepatorenal failure	
<b>Skin and subcutaneous tissue disorders</b>			Skin rash / pruritus	Urticarial reaction Toxic epidermal necrolysis Erythema nodosum Angioedema*	Acute generalised exanthematous pustulosis

MedDRA System Organ Class	Adverse events (frequency)				
	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10000 to < 1/1000 and very rare (< 1/10000)*	Not known (cannot be estimated from the available data)
Musculoskeletal and connective tissue disorders				Limb spasm	
Renal and urinary disorders				Renal failure	
Pregnancy, puerperium and perinatal conditions	Very common 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 tumor Uteroplacental apoplexy	
Reproductive system and breast disorders	Vaginal bleeding Uterine spasm	Prolonged post-abortion bleeding Spotting Severe hemorrhage Endometritis Breast tenderness Heavy bleeding	Hemorrhagic shock Salpingitis	Bilateral adnexal mass Intrauterine adhesion Ovarian cyst rupture Breast abscess Hematosalpinx Uterine rupture	
General disorders and administration site conditions	Fatigue Chill / fever Dizziness	Fainting		Anaphylaxis Periorbital edema 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 authorization 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 reaction via the Yellow Card Scheme

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

No case of overdose has been reported.

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.

## 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 antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10 mg/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 patient 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. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data is available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

When 1 mg vaginal gemeprost following 200 mg mifepristone is used, the efficacy rate in pregnancies 57 to 63 DA is 92.4% (95% confidence interval: 89.6 – 94.7%)

Failures are due to either incomplete abortion or to persisting pregnancy: in practical terms, whatever their nature, failure necessitate a surgical procedure (vacuum aspiration or dilatation and curettage).

Mifepristone binds to the glucocorticoid receptor. In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol. Glucocorticoid bioactivity (GBA) may be depressed for several days following a single administration of 200 mg 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

### 5.2 Pharmacokinetic properties

After oral administration of a single dose of 200 mg mifepristone is rapidly absorbed. 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 approx. 12 to 72 hours, and then the concentration is more rapidly reduced with a half-life of 18 hours. With radio-receptor analysis, the final half-life is shown to be up to 90 hours, including all mifepristone metabolites that can bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg 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 mono- and di-demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. The binding affinity of the metabolites to progesterone receptors is about 10 to 20% of that of mifepristone and it is not known whether they contribute to the pharmacological effects of mifepristone.

*In vitro* CYP3A4 appears as the isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77 %. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2E1) had apparently no action on mifepristone metabolism.

After administration of 600 mg radiolabeled mifepristone, 10% of the total radioactivity was recovered in urine and 90% in faeces.

#### 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<sub>max</sub> 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<sub>∞</sub> 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 (antiprogestrone, antigluocorticoid 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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Maize starch,  
Povidone (K30),  
Cellulose microcrystalline,  
Silica colloidal anhydrous  
Magnesium stearate.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Keep the blister in the outer carton in order to protect from light.

### **6.5 Nature and contents of container**

PVC/PVDC/Aluminum blister of 1 tablet.  
Pack sizes with 1 tablet and 30 tablets (as hospital pack).  
Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Nordic Group B.V. trading as Linepharma  
Siriusdreef 41  
2132 WT Hoofddorp  
The Netherlands

## **8. MARKETING AUTHORISATION NUMBER(S)**

PL 40621/0039

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

01/12/2015

**10. DATE OF REVISION OF THE TEXT**

20/02/2026