SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mifepristone 200 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200-mg mifepristone.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Mifepristone 200 mg tablets is available as Light yellow coloured, round, biconvex tablets debossed with “CC12” on one side and plain on other side with approximately 11mm in diameter and free from physical defects.

4 CLINICAL PARTICULARS

For termination of pregnancy, the anti-progesterone mifepristone and the prostaglandin analogue can only be prescribed and administered in accordance with the countries national laws and regulations.

4.1 Therapeutic indications

1- Medical termination of developing intra-uterine pregnancy.

In sequential use with a prostaglandin analogue, up to 63 days of amenorrhea (see section 4.2)**.**

2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.

3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*.

4- Labour induction in fetal death in utero.

In patients where prostaglandin or oxytocin cannot be used.

4.2 Posology and method of administration

Posology

1- Medical termination of developing intra-uterine pregnancy The method of administration will be as follows:

- Up to 49 days of amenorrhea:

Mifepristone is taken as a single 600 mg (i.e.3 tablets of 200 mg each) oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue: misoprostol 400 µg orally, or gemeprost 1 mg per vaginam.

Alternatively, 200 mg of mifepristone (i.e. 1 tablet of 200 mg) can also be used in a single oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam (see section 5.1. pharmacodynamic properties).

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).

- Between 50-63 days of amenorrhea

Mifepristone is taken as a single 600 mg (i.e. 3 tablets of 200 mg each) oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.

Alternatively, 200 mg of mifepristone (i.e. 1 tablet of 200 mg) can also be used in a single oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam (see section 5.1. pharmacodynamic properties).

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).

Information on the posology of misoprostol or gemeprost can be found in the respective product information.

2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.

Mifepristone is taken as a single 200 mg (1 tablet) oral dose, followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons

Mifepristone is taken as a single 600 mg (i.e. 3 tablets of 200 mg each) oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4- Labour induction in foetal death in utero

Mifepristone is taken as a single 600 mg (e.g. 3 tablets of 200 mg each) oral daily 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 of mifepristone.

Vomiting within 45 minutes after the intake could lead to a decrease in mifepristone efficacy: oral intake of a new mifepristone 600 mg dose (e.g. 3 tablets of 200 mg each) is recommended in this case.

Paediatric population

Only limited data are available on the use of mifepristone in adolescents.

Method of administration

Mifepristone tablets are for oral use only and should not be taken by any other route of administration.

4.3 Contraindications

This product SHOULD NEVER be prescribed in the following situations.

In all indications

- chronic adrenal failure,
- hypersensitivity to mifepristone or to any of the excipients listed in section 6.1, - severe asthma uncontrolled by therapy, - inherited porphyria.

In the indication: medical termination of developing pregnancy

- pregnancy not confirmed by ultrasound scan or biological tests,
- pregnancy beyond 63 days of amenorrhea,
- suspected extra-uterine pregnancy,
- contra-indication to the prostaglandin analogue selected.

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:

- pregnancy not confirmed by ultrasound scan or biological test, - pregnancy of 84 days of amenorrhea and beyond - suspected extra-uterine pregnancy.

In the indication: preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*

- contra-indications to the prostaglandin analogue selected

4.4 Special warnings and precautions for use

Warnings

Because of its abortifacient properties, mifepristone should never be used in a woman with an ongoing pregnancy who wants to complete it.

The age of the pregnancy must be determined from the questioning and the clinical examination of the patient. Uterine ultrasound is recommended.

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, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.

The pharmacokinetics, safety and tolerability of mifepristone 200 mg were investigated in women with moderate hepatic impairment versus healthy women participants with normal hepatic function. Statistical analyses of total AUC∞ and Cmax 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 is not recommended in patients with:

- ***Malnutrition***

- ***Hepatic failure***
- ***Renal failure***

1- Medical termination of developing intra-uterine pregnancy

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

- the necessity to combine treatment with a prostaglandin analogue to be administered at a second visit 36 – 48 hours after administration of this medicine,
- the need for a follow-up visit (3rd visit) within 14 to 21 days after intake of mifepristone in order to check for complete expulsion,
- the possible failure of the method, leading to a pregnancy 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.

• Risks related to the method

- Failures

The non-negligible risk of failure, which occurs in 1.3 to 7.5 % 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 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 about 12 days or more after mifepristone intake) which may be heavy.

Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The bleeding can occur very quickly after misoprostol intake, and sometimes later:

- In 60%, expulsion occurs within 4 hours following misoprostol intake
- In the remaining 40% of the cases, expulsion occurs within 24 to 72 hours following misoprostol intake.

Rarely the expulsion may occur before administration of the prostaglandin analogue (around 3% of the cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

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. This is bleeding that lasts longer than 12 days and/or that is heavier than the normal menstrual bleeding.

A follow-up visit must take place within a period of 14 to 21 days after the intake of mifepristone to verify by the appropriate means (clinical examination, together with beta-hCG measurement or ultrasound scan) 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.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an undiagnosed ectopic pregnancy, and appropriate treatment should be considered.

Since heavy bleeding requiring haemostatic curettage occurs in 0 to 1.4% 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.

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

- Infection

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.

2- Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of Mifepristone 200 mg tablets must be followed, 36 to 48 hours later and not beyond, by surgical termination.

• Risks related to the method

- Bleeding

The woman will be informed of the risk of vaginal bleeding which may be heavy, following intake of Mifepristone 200 mg tablets . She should be informed of the risk of abortion prior to surgery (although minimal). She will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.

Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with haemostatic disorders, hypocoagulability, or severe anaemia.

- Other risks

They are those of the surgical procedure.

Precautions for use 1- In all instances

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 200 mg tablets. Therapy should be adjusted.

Rhesus allo-immunisation

The medical termination of pregnancy requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures usually taken during any termination of pregnancy.

Contraception initiation after medical termination of pregnancy

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. Therefore, when a termination of pregnancy conducted by medical procedure is medically confirmed, it is recommended to start contraception immediately.

Other

The precautions related to prostaglandin analogues should also be followed.

2- Medical termination of developing intra-uterine pregnancy

Rare but serious cardiovascular accidents (myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported following the intra vaginal and intra muscular administration of a high dose of prostaglandin analogue. Misoprostol administered orally could also constitute a potential risk factor of acute cardiovascular events. For this reason, women with risk factors for cardiovascular disease (e.g. age over 35 years with chronic smoking, hyperlipidemia, diabetes) or established cardiovascular disease should be treated with caution.

3- For the sequential use of Mifepristone 200 mg tablets - Prostaglandin, whatever the indication

The precautions related to the prostaglandin used should be followed where relevant.

Method of prostaglandin administration

During intake and for three hours following the intake, the patient should, in principle, 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 counselled 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. Cmax 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 (Cmax 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 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 as phenytoin, phenobarbital, carbamazepine).

Therefore, in case a medical termination of developing intra-uterine pregnancy is to be done for 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 (misoprostol 400 µg orally, or gemeprost 1 mg per vaginam).

Effect of mifepristone on other medicinal products

In vitro and *in vivo* data indicate that mifepristone is an inhibitor of CYP3A4. Coadministration 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 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule. With subabortive doses, malformations were observed in rabbits, but not in rats, mice or monkeys. In clinical practice, rare cases of malformations of the extremity of lower limbs (out of them, club-foot) have been reported in case of mifepristone administered alone or associated with prostaglandins. One of the possible mechanisms might be amniotic band syndrome. However, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the risk to the foetus, the follow-up visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the follow-up 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, a careful ultrasound monitoring of the pregnancy, with a special attention to the limbs, must be established in a specialised centre.

Breastfeeding

Mifepristone is excreted in mother’s milk in small amounts. Consequently, mifepristone use 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

The frequencies of occurrence of side effects are classified as follows: Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1,000 to < 1/100) Rare (≥ 1/10,000 to <

1/1,000) Very rare (< 1/10,000)

Not known (cannot be estimated from the available data)

Infections and infestations

Common:

- Infection following abortion. Suspected or confirmed infections (endometritis, pelvic inflammatory disease) have been reported in less than 5% of women. *Very rare:*

- Very rare cases of serious or fatal toxic and septic shock (caused by *Clostridium sordellii* or *Escherichia coli*), which can be with or without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of unauthorised vaginal or buccal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication (see section 4.4. – special warnings and special precautions for use).

Nervous system disorders *Rare:*

- Headache Vascular disorders *Uncommon:*

- Hypotension (0.25%) Gastrointestinal disorders *Very common:*

- Nausea, vomiting, diarrhoea (these gastro intestinal effects related to prostaglandin use are frequently reported).

Common:

- Cramping, light or moderate.

Skin and subcutaneous tissue disorders

Uncommon

- Hypersensitivity: Skin rashes uncommon (0.2%). *Rare*

- Single cases of urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis have also been reported.

Very rare

- Angioedema *Not known*

- Acute generalised exanthematous pustulosis Reproductive system and breast disorders *Very common:*

- Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake. *Common:*

- Heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.4% of the cases. *Rare:*

- During induction of second trimester termination of pregnancy or labour induction for foetal death in utero within the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar. General disorders and administration site conditions *Rare:*

- Malaise, vagal symptoms (hot flushes, dizziness, chills), fever.

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: Yellow Card Scheme

Website: 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 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

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 women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandin. 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 to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

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

The success rate is around 95 % when 600 mg mifepristone is combined with misoprostol 400 µg orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98% up to 49 days of amenorrhea and 95% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially Mifepristone 200 mg tablets followed by a prostaglandin analogue, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of haemostatic curettage

In pregnancies up to 49 days of amenorrhea, comparative studies between 200 mg and 600 mg of mifepristone in combination with 400 µg misoprostol orally cannot exclude a slightly higher risk of continuing pregnancies with the 200 mg dose.

In pregnancies up to 63 days of amenorrhea, comparative studies between 200 mg and 600 mg of mifepristone in combination with 1 mg gemeprost vaginally suggest that 200 mg mifepristone may be as effective as 600 mg mifepristone:

Complete abortion rates with 200 mg and 600 mg were 93.8% and 94.3%, respectively, in women with < 57 days of amenorrhea (n=777. WHO 1993), and 92.4% and 91.7%, respectively, in women with 57 to 63 days of amenorrhea (n=896, WHO 2001).

• Rates of ongoing pregnancies with 200 mg and 600 mg were 0.5% and 0.3%, respectively, in women with < 57 days of amenorrhea, and 1.3% and 1.6%, respectively, in women with 57 to 63 days of amenorrhea.

Combinations of mifepristone with prostaglandin analogues other than misoprostol and gemeprost have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandin, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of foetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

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

Absorption

After oral administration of a single dose of 600 mg mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/l is reached after 1.30 hours (means of 10 subjects). After oral administration of low doses of mifepristone (20 mg), the absolute bioavailability is 69%.

Distribution

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha1-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.

Biotransformation

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Elimination

There is a non-linear dose response. 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 radio receptor assay

techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

Mifepristone is mainly excreted in faeces. After administration of a 600 mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the 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 Cmax 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. 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 (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, foetal anomalies were observed (cranial vault, brain and spinal cord). The effect was dose-dependent. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment. No evidence of teratogenicity was observed in postimplantation rat and monkey embryos exposed to mifepristone in vitro.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous (E551) Maize starch

Povidone (E1201) Magnesium stearate (E470b)

Cellulose microcrystalline (E460)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Alu-PVC-PVDC blister pack unit dose blister packs of 1, 3 x 1, 15 x 1 or 30 x 1 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Naari B.V

Kanaalstraat 12 B

5347 KM Oss

Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 46973/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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