APPROVED EUROPEAN SPC
JULY 6, 1999

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Therapeutic indications & Posology

The European SPC has used the following wording. Consequently, the initial wording used in France and referred to in Appendix 10.1.1 has been modified to reflect the harmonized EU SmPC.

The following countries have been included in the procedure of Mutual Recognition: Austria, Belgium, Denmark, Finland, France (Reference Member State), Germany, Netherlands, Spain.

1- **Medical termination of developing intra-uterine pregnancy.** In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

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

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

200 mg of mifepristone (one tablet), 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 *(beyond the first trimester)*.**

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) taken in a single 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.**

In patients where prostaglandin or oxytocin cannot be used.

600 mg of mifepristone (e.g. 3 tablets of 200 mg each) in a single oral daily dose, for two consecutive days.

In the other countries where the product has been approved the wording is the following.

Israel

- **Medical alternative to uterine suction for termination of intra-uterine pregnancy**:
  - up to and no later than 49 days of amenorrhea (seven weeks)
  - In sequential use with a prostaglandin analog, misoprostol 400µg per os administered 36 to 48 hours after Mifegyne intake.

  Only this indication has been approved at the moment.

Russia

- **Medical termination of pregnancy up to 42 days of amenorrhea**
  600mg of mifepristone in a single dose.

- **Medical termination of pregnancy up to 63 days of amenorrhea in association with a prostaglandin analog (misoprostol, gemeprost)**
  600mg of mifepristone followed 36 to 48hours later by gemeprost 1mg p.v.

- **Dilatation of the cervix uteri prior to a surgical termination of pregnancy up to 12 weeks**
  600mg of mifepristone in a single dose.

- **Preparation to the action of prostaglandins for termination of pregnancy between 13 and 20 weeks gestation for medical or social reasons**
  600mg of mifepristone followed 36 to 48hours later by gemeprost 1mg p.v., repeated every three hours until complete expulsion.

The indication Labour induction for foetal death in utero has not been approved in Russia.

Switzerland

The same text as in the EU has been approved for indications and posology with a slight difference in the wording of indication 1. **Medical termination of intra-uterine pregnancy.**

For the above-mentioned countries the section Contra-indications include the following:

In all indications

- chronic adrenal failure
- known allergy to mifepristone or to any component of the product
- severe asthma uncontrolled by therapy

In the indication: medical termination of developing intra-uterine pregnancy

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- 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 (according to legal requirements)
- suspected extra-uterine pregnancy

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

Labour induction in foetal death in utero

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

In Israel, the section on Contra-indications is different and include the following items:

1. Known allergy to mifepristone or to any component of the product
2. Suspected extra-uterine pregnancy
3. Pregnancy not confirmed by ultrasound scan
4. Chronic adrenal failure
5. Hemorrhagic disorders
6. Long-term corticosteroid therapy

7. Severe asthma uncontrolled by corticosteroid therapy
8. Cardiac disease
9. Hyperlipidemia
10. Diabetes
11. Patients on antipsychotic drug therapy
12. Pregnancy beyond 49 days of amenorrhea
13. As a special precaution, the medical method is not recommended for use in women over 35 years of age or who smoke more than 10 cig/ day
14. Know allergy to prostaglandins
15. Patients with or history of cardiovascular disease

The items 1, 2, 4, 5, 6 and 15 are included in the contra-indication section of the UK data sheet.

The items 5, 6, 13 have been moved into the precautions section of the EU SmPC and item 13 is worded "... women over 35 years of age **and** who smoke more than 10 cigarettes/day". 9 and 11 do not exist in any of the master data sheet, EU, UK of Swedish information. 10 is included in the Precaution for use of the Master Data Sheet.

In addition, the following conditions have been considered in the warnings section: hepatic failure, renal failure, malnutrition.

APPENDIX 10.2

UPDATED LABELINGS

APPENDIX 10.2.1.

MASTER DATA SHEET

Exelgyn Laboratories
6, rue Christophe Colomb
F-75008 Paris

MIFEGYNE®
200 mg
Mifepristone

Master Data Sheet

December 1999

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

- MIFEGYNE® 200mg, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- Mifepristone micronised ..... 200 mg

- Anhydrous colloidal silica .....
- Maize starch .....
- Povidone .....
- Microcrystalline cellulose .....
- Magnesium stearate .....

3. PHARMACEUTICAL FORM

- Light yellow, cylindrical, bi-convex tablets, for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Medical alternative to surgical termination of intra-uterine pregnancy.**

  In sequential use with a prostaglandin analogue, administered 36 to 48 hours after MIFEGYNE® intake (see Posology and Method of Administration):

  - misoprostol 400 µg orally (for pregnancies up to 49 days of amenorrhea),
  - or gemeprost 1 mg, vaginal pessary (for pregnancies up to 63 days of amenorrhea).

  Under these conditions, the association of mifepristone and prostaglandins leads to a success rate of about 95 per cent of the attempted pregnancy terminations.
  (See Warnings and Precautions for use)

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

  Pre-treatment with mifepristone facilitates the surgical step of the mechanical dilatation.

- **Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons.**

  The use of MIFEGYNE® allows a significant reduction of the prostaglandins doses required for the expulsion.

- **Labour induction in fetal death in utero**

  MIFEGYNE® administered alone leads to expulsion in about 60%, allowing avoidance, or reduction in the dose of prostaglandins. Therefore, it is indicated especially when prostaglandins are contra-indicated.

4.2 Posology and method of administration

1) **Medical alternative to surgical termination of intra-uterine pregnancy**

MIFEGYNE® must not be administered if there is doubt as to the existence and age of the pregnancy, or in case of extra-uterine pregnancy. The prescribing doctor should in any case perform an ultrasound scan and/or measure Beta-hCG before administration.

The method of administration which will be prescribed by the physician and applied in the presence of the practitioner or of a health professional will be as follows:

- 600 mg of mifepristone (i.e. 3 tablets of 200 mg each) is taken in a single oral dose, followed by

- 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400 µg orally (pregnancies up to 49 days of amenorrhea), or gemeprost 1 mg vaginally (pregnancies up to 63 days of amenorrhea).

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

- 200 mg of mifepristone (one tablet) in the presence of the physician or of a health professional, followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3) **Preparation for the action of prostaglandin analogs in the termination of pregnancy for medical reasons**

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) taken in a single oral dose, in the presence of the physician or of a health professional, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4) **Labour induction for expulsion of a dead fetus (fetal death in utero)**

- 600 mg of mifepristone, e.g. 3 tablets of 200 mg each, in a single 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.

4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

- Chronic adrenal failure
- Known allergy to mifepristone or to any component of the product
- Severe asthma uncontrolled by corticosteroid therapy
- Porphyrias

In the indication: medical alternative to surgical termination of intra-uterine pregnancy

- Pregnancy not confirmed by ultrasound scan or biological tests.
- Pregnancy beyond 49 days of amenorrhea with misoprostol or beyond 63 days of amenorrhea with gemeprost.
- Suspected extra-uterine pregnancy
- Contra-indications due to the prostaglandins:
  - Known allergy to prostaglandin,
  - Patients with or history of cardiovascular disease (angina, Raynaud's syndrome or disease, cardiac arrhythmias, cardiac failure, severe hypertension).

  (See Precautions for use)

Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons

- Contra-indications to prostaglandins where relevant.

Labour induction for expulsion of a dead fetus (fetal death in utero)

- Should prostaglandins combination be required, refer to contra-indications to the prostaglandin analogue selected.

4.4 Warnings and Precautions for use

Warnings

Specific national legal requirements

MIFEGYNE® and the prostaglandin analogues can only be prescribed and administered in accordance with the national legal requirements.

As a consequence, they can only be prescribed by a medical doctor and in a public or private hospital or centre (having approval to undertake terminations of pregnancies) in accordance with the national legal requirements.

The signature of an informed consent letter by the patient would certify that she has been fully informed about the method and its risks, except in the cases of preparation to the action of prostaglandins for pregnancy termination for medical reasons as well as for the labour induction for expulsion of a dead fetus (Fetal Death in Utero).

1) **Medical alternative to surgical pregnancy termination of intra-uterine pregnancy**

Failures

Unless abortion has already been completed, the use of MIFEGYNE® must be followed, 36 to 48 hours later, by a prostaglandin analogue administered either vaginally or orally, as mifepristone alone given without prostaglandins would lead to a failure rate of the method of at least 20 per cent.

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 MIFEGYNE® 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 hemostatic curettage

Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (about 9 days after MIFEGYNE® intake) which may be heavy.

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

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.

A follow-up visit must take place mandatorily within a period of **10 to 14 days** after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, Beta-hCG measurement, ultrasound scan, etc...) that expulsion has been completed and that vaginal bleeding has stopped (apart from light bleeding the disappearance of which should be checked within a few days).

Persistence of vaginal bleeding at this point could indicate incomplete abortion, or an unnoticed extra-uterine pregnancy, and an appropriate treatment should be considered.

Since heavy bleeding requiring hemostatic curettage occurs in up to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemorrhagic disorders with hypocoagulability , or with anemia.

The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anemia.

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

For the full efficacy of therapy, the use of MIFEGYNE® must mandatorily be followed, 36 to 48 hours later and not beyond, by surgical termination.

The woman must be informed of the risk of bleeding, which may be heavy, following mifepristone intake. She will be informed of the rare occurrence (0.9%) of expulsion prior to the surgical termination.

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.

3) Preparation for the action of prostaglandin analogs for termination of pregnancy for medical reasons

The administration of prostaglandins carries some risks; however pre-treatment with MIFEGYNE® has been shown to reduce the total dose of prostaglandins required. Moreover, the risks of other (mechanical) methods of termination for advanced pregnancies, beyond 12 weeks, have to be considered.

Precautions for use

1) In all instances

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

- In case of suspected acute adrenal failure, dexamethasone administration is recommended.

- Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3 to 4 days following MIFEGYNE® 's intake. Therapy should be adjusted.

  In the event of inhaled corticosteroid therapy, particularly in patients with asthma, it is recommended to adjust the treatment by doubling the dose during the 48 hours preceding mifepristone's administration and for about one week duration.

- In patients with Insulin-dependent Diabetes, the occurrence of gastro-intestinal disorders induced by the pregnancy itself or by the treatment, would require an adjustment of insulin therapy.

- During clinical trials, pregnancies occurred between fetal 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.

- As a precaution and in the absence of specific studies, mifepristone should not be used in patients with:
  - Renal failure
  - Liver failure
  - Malnutrition

2) **Medical alternative to surgical termination of intra-uterine pregnancy**

In any case of a pregnancy occurring on a intra-uterine device, this device must be removed before administration of MIFEGYNE®.

During the initial clinical trials, rare serious cardiovascular accidents similar to coronary spasm have been reported following the administration of a PGE_2 analogue (intra-muscular sulprostone). These events were reported in women over 30 years of age and smoking more than 10 cigarettes a day.

No such cases have been reported, since analogues of PGE_1 (gemeprost or misoprostol) have been used. The present experience is based upon 400,000 treatments of which about 320,000 used misoprostol and about 80,000 used gemeprost.

Therefore, as a special precaution, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

In any case, the risk of cardiovascular events must be taken into consideration when prostaglandins are used in association with mifepristone.

Method of prostaglandins administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be fitted with the appropriate cardiovascular monitoring and resuscitation equipment.

3) **For the sequential use of MIFEGYNE® - Prostaglandins, whatever the indication**

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

4.5 Interaction with other drugs and other types of interactions.

Associations to be avoided

- Non steroidal anti-inflammatory drugs (NSAIDs) including aspirin. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of NSAIDs. Use preferably non-NSAIDs analgesics.

4.6 Pregnancy and lactation

Patients must be informed that in the event of failure of the methods, the pregnancy is liable to continue to develop. The fetus may then be exposed to a risk of malformation.

In studies performed in animals, fetal anomalies have been observed in rabbits (skull lesions), but not in rats and mice. No teratogenicity was observed after in vitro exposure of monkey embryos to mifepristone. When the pregnancy continued after mifepristone alone or with prostaglandins, uncommon cases of malformations have been reported in the fetus or the infant. Malformations have also been reported after the use of prostaglandins alone.

The exact role of mifepristone, prostaglandin analogue, or coincidental event cannot be established.

It is essential that termination of pregnancy by another method be undertaken at a follow-up visit, in the event of such failure.

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

4.7 Effects or ability to drive and to use machines

Unknown

4.8 Undesirable effects

Very common	>1/10		
Common	>1/100	and	<1/10
Uncommon	>1/1000	and	<1/100
Rare	>1/10,000	and	<1/1000
Very rare	<1/10,000		

- Urogenital
  - Bleeding

    Bleeding occurs in almost all women and increases with the age of pregnancy at the time of termination.

    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4 of the cases.

- Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
- Uterine rupture has been uncommonly reported after prostaglandin intake for induction of second trimester termination of pregnancy of labour induction for fetal death in utero during the third trimester.

  The reports occurred particularly in multiparous women or in women with a cesarean section scar.

– Gastrointestinal

Nausea, vomiting, diarrhea, very common after prostaglandin intake.

– Cardiovascular

Uncommon hypotension (0.25%).

– Hypersensitivity and skin

Uncommon skin rashes (0.2%). Single cases of urticaria, of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

– Other systems

Rare cases of headaches, malaise, common vagal symptoms (hot flushes, dizziness, chills), and uncommon fever have been reported .

4.9 Overdose

Dose-ranging studies have shown that administration of single doses of mifepristone up to 2 g caused no unwanted reaction.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Any suggestion of acute intoxication, therefore, requires treatment in a specific environment, and if relevant with dexamethasone administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/
ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

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 are 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 up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98.7% up to 49 days of amenorrhea and 94.8% 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 MIFEGYNE® followed by a prostaglandin analog, 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 hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues 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 prostaglandins, 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.

042

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. 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.

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

5.2 Pharmacokinetic properties

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

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.

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

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.

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, 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

Anhydrous colloidal silica, maize starch, povidone, microcrystalline cellulose, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Blister pack (PVC and Aluminium foil and carton) containing 3 tablets.

6.6 Instructions for Use/Handling

The treatment procedure should be fully explained and completely understood by the patient.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT

December 1999.

044

MIF 007719

APPENDIX 10.2.2.

EUROPEAN SMPC APPROVED JULY 6, 1999

045

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIFEGYNE® 200 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200-mg mifepristone.

3. PHARMACEUTICAL FORM

Tablet.
Light yellow, cylindrical, biconvex tablets marked "167 B" on one side.

4. CLINICAL PARTICULARS

For termination of pregnancy, MIFEGYNE® and the prostaglandin can only be prescribed and administered in accordance with the countries laws and regulations.

As a consequence, they can only be prescribed by a medical doctor and in public or private hospital or centre (having approval to undertake termination of pregnancy). The product will be administered in the presence of the medical practitioner or of a delegated health professional.

If required by the afore mentioned laws and regulations, the patient should sign a letter of informed consent to certify that she has been fully informed about the method and its risks.

This timing of the first visit should take into account the requirement of some countries for a period of reflection prior to the abortion procedure.

4.1 Therapeutic indications

1- Medical termination of developing intra-uterine pregnancy.

In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

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 foetal death in utero.

In patients where prostaglandin or oxytocin cannot be used.

4.2 Posology and Method of Administration

1- Medical termination of developing intra-uterine pregnancy

The method of administration will be as follows:

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

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

200 mg of mifepristone (one tablet), 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

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) taken in a single 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

600 mg of mifepristone (e.g. 3 tablets of 200 mg each) in a single 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.

047

4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

In all indications

- chronic adrenal failure
- known allergy to mifepristone or to any component of the product
- severe asthma uncontrolled by therapy

In the indication: medical termination of developing intra-uterine pregnancy

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- 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 (according to legal requirements)
- suspected extra-uterine pregnancy

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

Labour induction in foetal death in utero

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

4.4 Special warnings and special precautions for use

Warnings

In the absence of specific studies, MIFEGYNE® is not recommended in patients with:

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

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 prostaglandin to be administered at a second visit,
- the need for a control visit (3rd visit) within 10 to 14 days after MIFEGYNE's intake 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 MIFEGYNE®.

- 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.

- 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.

  - Bleeding

    The patient must be informed of the occurrence of prolonged vaginal bleeding (up to 12 days after MIFEGYNE® intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

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.

A follow-up visit must take place within a period of 10 to 14 days after administration of MIFEGYNE® 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 hemostatic 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 hemostatic disorders with hypocoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anaemia.

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

For the full efficacy of therapy, the use of MIFEGYNE® 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 MIFEGYNE's intake. 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.

050

- Other risks

  They are those of the surgical procedure.

3- In all instances

The use of MIFEGYNE® 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.

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 MIFEGYNE's intake. 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). Use preferably non-NSAI analgesics.

2- Medical termination of developing intra-uterine pregnancy

Rare serious cardiovascular accidents have been reported following the intra muscular administration of the prostaglandin analogue sulprostone (withdrawn in 1992). No such cases have been reported since analogues of PGE_1 (gemeprost or misoprostol) have been used. For these reasons and as a special precautionary measure, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

Method of prostaglandin administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be equipped with the appropriate equipment.

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3- For the sequential use of MIFEGYNE® - Prostaglandin, whatever the indication

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

4.5 Interaction with other medicinal products and other forms of interactions

No studies to investigate possible interactions between mifepristone and other drugs have been carried out.

4.6 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 subabortive 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.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special 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 is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultra-sonographic monitoring of the pregnancy will be established.

Lactation

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

4.7 Effects on ability to drive and to use machines

Not known.

4.8 Undesirable effects

Most frequently reported undesirable effects

- Urogenital
  - Bleeding

    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.
  - Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
  - During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during 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.
- Gastrointestinal
  - Cramping, light or moderate.
  - Nausea, vomiting.
- Undesirable effects related to prostaglandin use: nausea, vomiting or diarrhoea, and rarely hypotension (0.25%)

Other undesirable effects

- Hypersensitivity and skin
  - Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
  - Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.
- Other systems

  Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

4.9 Overdose

After extensive clinical use, no reports of acute intoxication have been reported.

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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

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/
ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

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 are 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 up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98.7% up to 49 days of amenorrhea and 94.8% 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 MIFEGYNE® followed by a prostaglandin analog, 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 hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues 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 prostaglandins, 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. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. 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.

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

5.2 Pharmacokinetic properties

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

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.

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

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.

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, 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

Colloidal silica anhydrous, maize starch, povidone, magnesium stearate, microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

3 tablets in blister (PVC / Aluminium).

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

EXELGYN
6, rue Christophe Colomb
75008 PARIS
France

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

APPENDIX 10.3

STATUS OF CLINICAL TRIALS

APPENDIX 10.3.2

NAMED-PATIENT STUDIES

NAMED PATIENTS

Named-patient studies
November 1999

55	with unresectable meningioma
3	with leiomyosarcomas
4	with adrenal tumors (Cushing syndromes)
1	with desmoid tumor
3	with recurrent endometrial cancer
5	with breast cancer
71	**Patients**

APPENDIX 10.4

LINE LISTINGS OF INDIVIDUAL CASE HISTORIES

APPENDIX 10.5

LIST OF REFERENCES

REFERENCES

1. H de Verneuil, JC Deybach, N Phung, V Da Silva, Y Nordmann
Study of anaesthetics agents for their ability to elicit porphyrin biosynthesis in chick embryo liver.
Biochemical Pharmacology 1983; 32(6): 1011-1018

2. B Elul, C Ellertson, B Winikoff, K Coyaji
Side effects of mifepristone-misoprostol abortion versus surgical abortion.
Contraception 1999; 59: 107-114

3. EV Gouk, K Lincoln, A Khari, J Haslock, J Knight, DJ Cruickshank
Medical termination of pregnancy at 63 to 83 days gestation.
BJOG 1999; 106: 535-539

4. JT Jensen, SJ Astley, E Morgan, MD Nichols
Outcomes of suction curettage and mifepristone abortion in the United States.
Contraception 1999; 59: 153-159

5. EA Shaff, SH Eisinger, LS Stadalius, P Franks, BZ Gore, S Poppema
Low-dose of mifepristone 200 mg and vaginal misoprostol for abortion.
Contraception 1999; 59: 1-6

6. PW Ashok, A Templeton
Nonsurgical mid-trimester termination of pregnancy: a review of 500 consecutives cases.
BJOG 1999; 106: 706-710

7. O Heikinheimo, S Ranta, S Grunberg, P Lähteenmäki, IM Spitz
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Metabolism, 1997; 46(3): 292-296

8. PM Stenlund, G Ekman, AR Aedo, M Bygdeman
Induction of labor with mifepristone. A randomized, double-blind study versus placebo.
Acta Obstet Gynecol Scand 1999; 78: 793-798

REFERENCE 1

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Alterations in the pituitary-thyroid and pituitary-adrenal Axes Consequences of long-term mifepristone treatment.

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REFERENCE 8

PM Stenlund, G Ekman, AR Aedo, M Bygdeman

**Induction of labor with mifepristone.
A randomized, double-blind study versus placebo.**

Acta Obstet Gynecol Scand 1999; 78: 793-798

APPENDIX 10.6.

UPDATED LISTING ON ONGOING PREGNANCIES FROM 1987 TO 1999

	MIF ALONE	MIF+ MIS	MIF+ SUL	MIF+ UNK	MIF+ PG	MIF+ GEM	TOTAL
Normal Babies	12	13	2	4	2	4	37
Malformation at Term	0	0	0	0	0	3	3
MALF / TToP	1	0	0	0	0	5	6
Delayed Spont. Abortion	3	1	0	0	0	0	4
TToP UNK	4	3	0	0	2	0	9
TToP Normal Foetus	2	6	1	1	1	0	11
UNK/USNL	3	4	0	2	3	0	12
UNK	13	9	1	2	0	0	25
TOTAL	38	36	4	9	8	12	107

Update 30 November 1999

LEGENDS

MIF= mifepristone
MIS= misoprostol
SUL= sulprostone
GEM= gemeprost
PG= prostaglandin (unspecified)
UNK= unknown
TToP= Therapeutic Termination of Pregnancy
USNL= Ultrasound Normal (at second or third trimester)
Delayed Spont Abortion= Delayed Spontaneous Abortion
MALF/TToP=Malformation with therapeutic termination of pregnancy

APPENDIX I

ONGOING PREGNANCIES

I	N°	Case Number	Date MIF or Week of Am.	PG	TERM	DOSE	CAT	TYPE	OUTCOME
1		PMIF0001.87FR$	22/08/87, 5 w	NO		400	TTOPM	Sirenomelia, *	
2	G1	PMIF0002.88FR$	18/10/88, 6 w	SUL		600	TTOP	**	NL Foetus
3	2	PMIF0001.89FR	20/05/89, 7 w	YES		600	TTOP	**	NL Foetus, Male
4	3	PMIF0002.89FR	8/2/89	NO	TERM	600	NL	***	Female
5	5	PMIF0004.90FR	3/2/90	NO		600	TTOP	***	NL Foetus
6	8	PMIF0003.89FR$	End 1989, 6-7 w	NO	TERM	400	NL	Published, Pons,*,***	Male
7		PMIF0001.90GB£	8 w	NO	TERM	600	NL	*	Male
8		PMIF0002.90GB£	8 w	NO	TERM	600	NL	*	Male
9		PMIF0003.90GB£	9 w	NO	TERM	600	NL	*	Female
10	7	PMIF0005.90FR	1990	NO		600	TTOP	At 2 months, U	NL Foetus
11	9	PMIF0006.90FR	21/02/90, 5-6 w	SUL		600	U	*,***, SA?	
12	10	PMIF0007.91FR	June 1991	SUL	TERM	600	NL	*, **	Male
13		MIF0029.91FR/OS	Unk	U	TERM	600	NL	U	
14		MIF0030.92FR/OS	Unk	U		600	U	***	NL 2nd semester
15	11	PMIF0008.91FR	1991	NO	TERM	600	NL	*	
16	12	PMIF0009.92FR/RA	?	NO		600	U	***	NL 2nd semester
17	13	PMIF0004.92FR$	CT, 47OA	NO		600	U	***	
18	14	PMIF0010.92FR	15/04/92, 7 w, Trinordiol	SUL	TERM	600	NL	*	Female
19		PMIF0002.93GB	8 w	YES		600	U	***	NL 2nd semester
20	15	PMIF0011.92FR/RA	24.07.92, 5 w	YES		600	TTOP	*, ***	7,5
21	16	PMIF0012.93FR	?	MIS		600	TTOP	***	NL Foetus
22	17	PMIF0013.93FR/RA	6/7 w a	MIS		600	U	Lost to FU	NL 2nd semester
23	18	PMIF0014.93FR	?	NO		600	TTOP	***	
24	19	PMIF0015.93FR	22/03/93, 7 w 2 d	MIS		600	U	***	
25		PMIF0003.93GB		GEM	TERM	600	ABN	Bilateral talipes, *	
26	20	PMIF0016.93FR/RA	17/03/93(vomits) Twice 3 gp	NO		1200	U	U	
27	21	PMIF0017.93FR	? 93	MIS		600	U	U	
28	22	PMIF0018.93FR		MIS	TERM	600	NL	*	
29	23	MIF/PG0024.93FR	? 09/93, 5 w	NO		600	SA	*	Bled since MIF, 5 m
30	24	MIF/PG0026.93FR	24/11/93 at 8w	MIS		600	SA	*	
31	25	MIF0001.94FR$	At 7 w. of amen.	MIS		600	U	Unsure at start	
32		MIF0001.94GB		NO		600	U	U	
33	26	MIF/PG9011.93GB$	21/09/92, 9 w 2 d	GEM	TERM	600	ABN	Finger nail defect (3), **	Oral Contraceptive.
34		MIF/PG0001.93SE	48 d	GEM	TERM	600	NL	Premature birth/cesarean	DMPA, Male
35	27	MIF0003.94FR	?	YES	TERM	600	NL	**	Male
36	28	MIF0004.94FR	5/1/94	YES		600	U	**, US Nl, Lost to FU	NL 2nd semester
37	29	MIF0005.94FR	? 6,5 w of a	U		600	U	U	NL 2nd semester
38		MIF0005.94.GB		GEM	TERM	600	NL	U	
39	30	MIF/PG0029.93FR	25/06/93 6 w of a	MIS	TERM		NL	U	Male
40	31	MIF0009.94FR	24/03/94	MIS		600	TTOP	***	NL Foetus, 25 w
41	32	MIF0013.94FR	17/06/94 à 52 d of ame.	NO		200	U	*	
42	33	MIF0017.94FR	7,5 w of a.	MIS		600	TTOP	unsure	Foetus unassessable
43	34	MIF0021.94FR	7 w of ame.	MIS	TERM	600	NL	*	Female
44	35	MIF0022.94FR$	26/08/93, 6 w	MIS	TERM	600	NL	At 3 Mths (Hepatitis...)	Other medicat, Fem
45	36	MIF0003.95FR	1995	NO		600	TTOP	*	
46		MIF0003.95GB£	8w of pregnancy	GEM		600	TTOPM	**, Talipes Equinovares	OC

47	37	MIF0011.95FR	?	U			U	U	
48	38	MIF0005.95FR	06.03.95	NO		600	U	*	
49	40	MIF0008.95FR	?	MIS		600	TTOP	***	NL Foetus
50	41	MIF0009.95FR	13.03.95, 7 w, in fact 11 w	GEM	TERM	600	NL	*?	
51	42	MIF0012.95FR/RA	7 w of amc	YES			TTOP	*	
52	43	MIF0013.95FR	27.06.95	MIS		600	TTOP	U	
53	44	MIF0015.95FR	18.04.94, 6 w	MIS	TERM	600	NL	U	Male
54	45	MIF0019.95FR/RA	mid-july 95	NO	TERM	600	NL	***	
55	46	MIF0021.95FR	Beginning dec. 95, 5 w of a.	MIS	TERM	600	NL	*	Female
56	47	MIF0004.96GB	13.11.95 7w pregnancy	GEM		600	TTOPM	Acheiria/talipes eq/toes abn/,**	Mandibula hypo.
57	48	MIF0005.96FR	Unk., 5.5 w of a.	MIS		600	U	*, ***	NL 2nd semester
58	49	MIF0007.96FR/RA	30.05.96	MIS		600	U	***	
59	50	MIF0003.96SE	26.06.96	GEM		600	TTOPM	Anencephaly, talipes eq	
60	51	MIF0001.97FR	12.12.96	NO		600	NL	***	Female
61		199500383RU (FR)	24/04/93, 55 d of amc.	MIS			TTOP	U	NL Foetus
62	52	199710066RDF	1/4/1997 6/7w of amc.	NO		600	TOP	*	
63	53	199710097RDF	27.01.97(4w of preg)	YES			NL	*	
64	54	199710379RDF	30.06.97	NO		600	U	*	
65	55	199710378RDF	11w	U		600	TTOP	*	NL Foetus
66	56	199710383RDF	U <7w	U		600	U	U	
67	57	199710467RDF	6 w	MIS		600	TTOP		NL Foetus
68	58	MIF0001.97SE	8 w 4 d	GEM?	TERM	600	ABN	heart malformation, *	
69	59	S970001GBMIF1	6-7 w	GEM		200	TTOPM	Cerebellum atrophy, *	
70	61	S980002F/MIF1	6 w	MIS	TERM		NL	U	
71		S980001GB/MIF1	9 w	MIS	TERM	200	NL	**	Male NL
72		S980004F/MIF1	7 w	MIS		600	U	***	US NL at 18 w
73		S980005F/MIF1	6-7 w	NO		600?	U	***	
74		S980009F/MIF1	6 w	MIS		?	U		?
75		S980011GB/MIF1	7 w	GEM	TERM	200	NL	***	NL Male
76		S980012GB/MIF1	8 w 1 d	MIS		200	TTOP	**	At 16 w No anomaly
77		S980013F/MIF1	14.5 w	?	?	?	NL	?	NL Male
78		S980014F/MIF1	8 w	?	?	?	NL	?	Female NL
79		S980015F/MIF1	16 w + 2 d	?	?	?	NL	?	NL
80		S980016F/MIF1	9 w + 3 d	MIS		400	NL	?	NL at 31 w
81		S980017GB/MIF1	8-9 w	GEM		200	TTOPM	***, Hydroceph, cleft P.	Cyclopia, Talipes
82		S980018FR/MIF1	6 w	MIS	TERM	600	NL		Male NL
83		S980020GB/MIF1	13 w	NO	TERM	600	NL	*	NL delivery
84		S990004F/MIF1	7.5 w	MIS	TERM	600	NL	***	Male NL
85		S990005F/MIF1	6.5 w	MIS		600	TTOP	***, US Viable at 14 w	No exam
86		S990006GB/MIF1	14 w	NO	SA	200	SA	*	SA
87		S990009GB/MIF1	8 w	NO		200	NL	*	Male NL
88		S990013GB/MIF1		NO		200		*	
89		S990007F/MIF1	8 w Am.	MIS				*	
90		S990008F/MIF1	7 w	MIS					
91		S990015F/MIF1	6 w of pregnancy	NO		600		*, US NI at 17 w	
92		S990016F/MIF1	8 w	NO		600		**, US, NI	
93		S990019GB/MIF1	8 w Am	MIS		200		*, US, Viable preg	
94		S990020GB/MIF1	8 w 6 days Am.	MIS		200		***	NI male baby
95		S990021GB/MIF1	7 w Am.	MIS				*	NI baby
96		S990022F/MIF1	7 w Am.	PG				15 w US NI	

97		S990023GB/MIF1		NO			TToP	*, Intrauterine death	
98		S990024GB/MIF1	8 w preg.	NO		200		**, US dead fetus, delayed SA	
99		S990025GB/MIF1	8 w Preg	MIS		200			
100		S990026GB/MIF1	21 w preg.	NO		200		*	
101		S990027GB/MIF1	8 w Am.	MIS		600			
102		S990028GB/MIF1	15 w Am.	NO		200		*,	
103		S990029GB/MIF1	8 w Am.	NO		200		*,	
104		S990031GB/MIF1	21 w preg	NO				*,	
105		S990032GB/MIF1	Trisomy	NO		600		*,	
106		S990035GB/MIF1$	13-21 w	NO		200		*	NI Baby
107		S990036GB/MIF1$	13-21 w	NO		200		*	NI Baby

Summary table of ongoing pregnancies

Abbreviations: ABN (Abnormality at term), Am or ame (amenorrhea), Cat (category), GEM (Gemeprost), MIF (Mifepristone), MIS (Misoprostol), NL (normal), OC (oral contraceptive).OUT (Outcome), PG (Prostaglandins), SA (spontaneous abortion), SUL (Sulprostone), TToP (Therapeutic Termination of Pregnancy), TToPM (Therapeutic Termination of Pregnancy with malformation), U or UNK (Unknown), w (weeks), * (changed her mind), **(diagnosis error), *** (did not return), TOP (Surgical early termination of pregnancy)

Appendix 2

Appendix F

Feminist Majority Foundation
Mifepristone Compassionate Use Program
1600 Wilson Blvd., Suite 801
Arlington, VA 22209
(703) 841-0540
Fax: (703) 522-2219

MIFEPRISTONE IN THE TREATMENT OF UNRESECTABLE MENINGIOMA COMPASSIONATE USE

INVESTIGATOR: _____

INVESTIGATOR'S ADDRESS: _____

_____

PHONE: _____ FAX: _____ E-MAIL: _____

IND #: _____ DATE ISSUED: ___/___/___

INDICATION: _____

DOSAGE: _____ SCHEDULE: _____

PROTOCOL/REFERENCES/CITATIONS: _____

_____

_____

PRETREATMENT ASSESSMENT

PATIENT: _____ SEX: M or F _____

DATE OF BIRTH (mm/dd/yy): ___/___/___ WEIGHT (Kg): _____ HEIGHT (cm): _____

MAJOR MEDICAL OR SURGERY HISTORY: YES _____ NO _____

If yes, give details: _____

MAJOR GYNECOLOGICAL SURGERY: YES _____ NO _____

If yes, give details: _____

LAST MENSTRUAL PERIOD (mm/yy): ___/___/___

CURRENT DISEASE (other than the meningioma):

_____

CURRENT TREATMENT: YES _____ NO _____

If yes, give details: _____

_____

CHARACTERISTICS OF THE MENINGIOMA

Date of discovery (mm/dd/yy): ___/___/___ Localization: _____

PREVIOUS TREATMENT(S): YES _____ NO _____

If yes, Surgical treatment: YES _____ NO _____

If yes, Number of surgical events: _____

Date(s) (mm/dd/yy): ___/___/___

___/___/___

___/___/___

Known histology? YES _____ NO _____

If yes, give details: _____

Progesterone receptors YES _____ NO_____

Medical treatment YES _____ NO _____

If yes:	Type	Start (mm/dd/yy)	End (mm/dd/yy)
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

Radiotherapy: YES _____ NO _____

Start date (mm/dd/yy): ___/___/___

Duration and total dose: _____

CLINICAL SYMPTOMS OF THE MENINGIOMA: YES _____ NO _____

If yes, give details: _____

_____

CT OR MRI SCANS ASSESSING MENINGIOMA PROGRESSION DURING PAST TWO YEARS

1st examination date (mm/dd/yy): ___/___/___

Results: _____

Last examination date (mm/dd/yy): ___/___/___

Results: _____

EVALUATION OF THE MENINGIOMA IN THE PAST 2 YEARS, give details:

_____

_____

LABORATORY INVESTIGATIONS: date (mm/dd/yy) ____/____/____

CBC Hemoglobin _____.___
Hematocrit _____.___
Erythrocytes _____.___
Leucocytes _____.___
Platelets _____
Fasting blood glucose _____.___
Creatinine _____.___
Sodium _____
Potassium _____

SGOT (ASAT) (UI/l) _____ Upper range _____ Of normal value
SGPT (ALAT) (UI/l) _____ Upper range _____ Of normal value
Alkaline phosphateses (UI/l) _____ Upper range _____ Of normal value
Total bilirubin _____ Upper range _____ Of normal value

T3 _____ Normal values: _____Units
T4 _____ Normal values: _____Units
TSH _____ Normal values: _____Units

TREATMENT WITH MIFEPRISTONE

Date of onset (mm/dd/yy): ____/____/____ Dose mg/d: _____

Date (mm/dd/yy): ____/____/____

Signature of investigator: _____

Please return a copy of this form to Medical Director, Mifepristone Compassionate Use Program, Feminist Majority Foundation, 1600 Wilson Blvd., Suite 801, Arlington, VA 22209.

Danco Laboratories, LLC

April 20, 2000

ORIGINAL

ORIG AMENDMENT

BC

Reviewed /S/ 4/27/00

Office of Drug Evaluation III
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 044 - Submission of Updated and Additional Stability Data

Dear ———

In our response (Amendment 043 dated March 30, 2000) to Drug Product Comment #2 of the Approvable Letter dated February 18, 2000, we indicated that in April we would have additional stability data on the two Danco Drug Product batches produced:

- Six-month accelerated and six-month long-term on the second Drug Production Batch, Lot #99007, and
- Nine-month long-term on the first Drug Production Batch, Lot #99005.

These new data are enclosed as Attachment 1 together with copies of prior stability data on the same batches for your reference. In addition, we have updated with the new data, the graphs originally presented in our Amendment 040 comparing the stability data for our Drug Product to Roussel Drug Product. These graphs are enclosed as Attachment 2. Danco produced Drug Product continues to demonstrate good stability and the results remain comparable to the original Roussel Drug Product. These data further support our proposal for a ——month initial expiry date as requested in our previous response to Drug Product Comment #2, which is enclosed as Attachment 3 herein for your reference.

Drug Product point #10 of the December 14, 1999 FDA Information Request Letter stated that "It is recommended that the ———— of mifepristone be monitored during stability testing". In our response to that point in Amendment 040 dated January

28, 2000 we indicated that test would be performed on the six-months accelerated storage samples of the first three stability batches.

We have now completed studies on the first two Drug Product Batches, Lot #'s 99005 and 99007, and the results are enclosed as Attachment 4. They confirm that the diffraction pattern is solely for . This reaffirms the stability of this product and its even under the stress conditions of 40°C and 60% humidity for six months. We will provide results for the third Drug Product batch in due course.

For your reference, we are enclosing relevant portions of prior submissions on stability as Attachment 5.

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

President and Chief Executive Officer

/dns
Enclosures

cc: Sandra P. Arnold – Population Council
Nancy L. Buc, Esq. – Buc & Beardsley

Frederick H. Schmidt – Population Council

Patricia C. Vaughan, Esq. – Population Council

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	April 20, 2000
TELEPHONE NO. *(Include Area Code)* (212) 339-0663	**FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

1230 York Avenue
New York, NY 10021

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (Chemical Abstracts) - (11β,17β)-11-[(4-Dimethylaminoethoxy)phenyl]-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 007787

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	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
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	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Submission of Updated and Additional Stability Data

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick M. Schmidt for	Sandra P. Arnold, Vice President	4/20/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Dag Hammarskjold Plaza, New York, NY 10017	(212) 339-0663

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

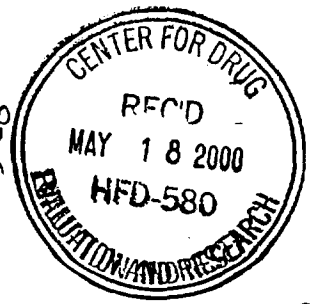
FORM FDA 356h (7/97)

Danco Laboratories, LLC

May 17, 2000

ORIGINAL

Review 9/27/00



ORIG AMENDMENT

BC

Office of Drug Evaluation III
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 047 - Additional Information on [redacted] Profile for Roussel Drug Product and Danco Stability Commitment

Dear

This Amendment 047 provides information requested in the FDA Teleconference Minutes dated April 25, 2000 concerning:

1) The commitment to develop [redacted] of Drug Substance (See Attachment A)

2) The revised [redacted] tests of Roussel Drug Product which establish a link to Danco Drug Product to allow for [redacted] initial expiry dating of the Danco Drug Product (See Attachment B)

3) The revision in the stability commitment to include the use of long-term data collected on the Danco pre-approval Drug Product batches for post-approval extension of the expiry dating for Danco Drug Product (See Attachment C).

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

[redacted]

President and Chief Executive Officer

REVIEWS COMPLETED

ONI ACTION

☐ LETTER ☐ N A I ☐ MEMO

DATE

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is [redacted]

/dns
Enclosures

cc: Sandra P. Arnold – Population Council

Nancy L. Buc, Esq. – Buc & Beardsley

Frederick H. Schmidt – Population Council

Patricia C. Vaughan, Esq. – Population Council

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	May 17, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(212) 339-0663	(212) 980-3710

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

One Dag Hammarskjold Plaza
New York, New York 10017

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
11β-[*p*-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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MIF 007791

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	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
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	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Additional Information on Cyrstal Form, Impurity Profile for Roussel Drug Product and Danco Stability Commitment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
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5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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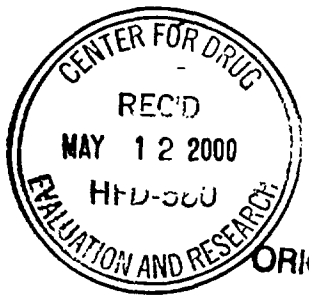
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick A. Sokol for	Sandra P. Arnold, Vice President	5/17/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Dag Hammarskjold Plaza, New York, NY 10017	(212) 339-0663

Danco Laboratories, LLC

May 11, 2000

Received 9/27/00



ORIG AMEN

BC

Office of Drug Evaluation III
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 046 - Methods Validation Package Supplement

Dear

This Amendment 046 contains five copies of the Certificate of Analysis for the Drug Substance working reference standard not included in Amendment 045, the Methods Validation package submitted May 3, 2000.

Please insert one of the enclosed Certificate of Analysis copies into each of the five copies of Amendment 045 behind the tab labeled "HuaLian Ref. Standard" and remove the blank page entitled "This Page Will Be Inserted When the Data Is Available".

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

President and Chief Executive Officer

Enclosures
cc: Sandra P. Arnold – Population Council

Nancy L. Buc, Esq. – Buc & Beardsley

- Danco Laboratories, LLC

Frederick H. Schmidt – Population Council

Patricia C. Vaughan, Esq. – Population Council

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
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Population Council	May 11, 2000
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(212) 339-0663	(212) 980-3710

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One Dag Hammarskjold Plaza
New York, New York 10017

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
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APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 007794

Danco Laboratories, LLC

May 3, 2000

ORIGINAL

Reviewed 5/22/00

Office of Drug Evaluation III
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 045 - Methods Validation Package

Dea

This Amendment 045 contains the Methods Validation Package requested by ' in a guidance teleconference held on April 26 and confirmed in the FDA minutes of that teleconference.

All requested information has been included with the exception of the certificate of analysis for the reference standard from the drug substance manufacturer. This document will be forwarded to the FDA as soon as we receive it from China. Additionally, please note that we have used the only available drug substance manufactured by Roussel as the Roussel reference standard.

We await instructions for shipping the samples of drug substance, impurity and drug product to the designated laboratories. Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely.

President and Chief Executive Officer

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61.** Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

/dns
Enclosures

cc: Sandra P. Arnold – Population Council
Nancy L. Buc, Esq. – Buc & Beardsley

FDA

Danco Laboratories, LLC
Frederick H. Schmidt – Population Council

Patricia C. Vaughan, Esq. – Population Council

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
One Dag Hammarskjold Plaza
New York, NY 10017

JUN 23 2000

Dear Ms. Arnold:

We acknowledge your June 12, 2000 request for a meeting to discuss the drug review for mifepristone. FDA categorizes meetings into three types:

Type A: A meeting that is necessary for an otherwise stalled drug development program to proceed.
Type B: A meeting described under drug regulations (e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2/Pre-Phase 3, Pre NDA).
Type C: All meetings other than those that qualify for Type A or B.

Based on the purpose, objectives, and proposed agenda, we consider the meeting to be a Type C. This meeting has been scheduled for:

Date:	July 19, 2000
Time:	9:00 am
Location:	Parklawn Building, Conference Center, Room "Potomac"
CDER participants:	

The background information for this meeting should be received by the Agency at least 2 weeks prior to the meeting. If we do not receive it by July 5, 2000, rescheduling of the meeting may be necessary.

If you have any questions, contact the undersigned

Sincerely,

/S/ 6/21/00

Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
HFD-580/NDA 20-687
HFD-580/Div Files
HFD-
Draft
Initial
final:
filena

GENERAL CORRESPONDENCE (MEETING TYPE)

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA 20-687, Mifepristone Tablets, 200 mg

Through: [redacted] - 6/20/00

From: [redacted] 6/20/00

Date: June 20, 2000

Re: Teleconference with [redacted] from Danco Laboratories, LLC

I contacted [redacted] from Danco concerning the process changes he faxed to me on June 16, 2000 and discussed at the June 19, 2000 teleconference. I requested that he provide the batch numbers and manufacturing dates of all the drug substance batches manufactured by Shanghai HuaLian prior to implementing those process changes and after implementing those changes. He informed me that the characterization data provided for the three batches (# 990101, 990102, 990103) in the NDA were manufactured prior to the process changes. I requested that the following data be provided for at least three post-change batches: 1) [redacted], 2) [redacted] 3) [redacted] including the [redacted] and 4)

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580 [redacted]
HFD-580 [redacted]

Filename: [redacted]

Teleconference Minutes

Date: June 7, 2000 **Time:** 4:30 – 4:50 pm **Location:** Parklawn, 13B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Discussion of Press coverage

Meeting Chair:

External Lead:

Meeting Recorder:

FDA Attendees:

r, Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER), FDA

Division of Reproductive and Urologic Drug Products

External Attendees:

The Danco Group
Sandra Arnold, Population Council
Nancy Buc, Buc and Beardsley

Meeting Objective: To clarify FDA comments and recommendations from the June 1, 2000 teleconference, to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.

Discussion:

Restricted Distribution

- FDA clarified with Population Council, Danco and Ms. Buc that the sponsor understood that a **public** registry of physicians was not proposed by FDA; rather, the FDA has proposed qualifications for physicians to ensure that recipients of the drug product are adequately trained for the safe use of this drug product; the sponsor's proposal for a distribution system, submitted in response to the approvable letters, only provided for the physical handling of the drug product; thus, in keeping with the recommendations of the July 1996 Advisory Committee and in order to advance the review of this application FDA provided recommendations for sponsor's consideration; sponsor concurred that this was also their understanding of the FDA proposals
- today's Press coverage described a "public registry" implying that qualified physicians could be readily identified and the list of those physicians could be publicly available; Population Council and Danco stated that their public statements only described the FDA recommendations as "more restrictive than expected", and that they did not provide any information about a public registry