3.1 Assay methods

Various assay methods have been employed in the measurement of serum mifepristone; these include radioimmunoassay (RIA), radioreceptor-assays (RRA) [27] and assays based on high-performance liquid chromatography (HPLC) [12].

Translator's Note:

1. *As requested, pages 49 through 95 are not translated.**

2. *The page numbers mentioned in the lexicon for the appendices refer to page numbers located on the upper right corner of the French text.*

***PC Comment: this refers to the Study Documentation which had been previously translated and was also included in the initial NDA 20-687 submission, March 14, 1996, Volume 108, pages 86-129. A copy of these documents are included on the following pages 56 through 99 of this Clinical Report.**

FF/91/486/14 - mifepristone
ROUSSEL Laboratories
Medical Division

Protocol FFR/91/486/14

EFFICACY AND SAFETY OF MIFEPRISTONE (RU 486) AT THE DOSE OF 600 MG IN A SINGLE ADMINISTRATION IN COMBINATION WITH MISOPROSTOL AS AN ALTERNATIVE TO UTERINE ASPIRATION FOR INTERRUPTION OF PREGNANCIES AGED LESS THAN OR EQUAL TO 49 DAYS OF AMENORRHEA

APPEARS THIS WAY

May 1991

FF/91/486/14 - mifepristone

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mifepristone-misoprostol
No. FRR/91/486/14

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ON ORIGINAL

1. INTRODUCTION

Mifepristone (RU 486, Mifégyne®) is an anti-progesterone compound synthesized by ROUSSEL UCLAF. Prior studies have shown that it is capable by itself of interrupting approximately 80% of pregnancies aged less than or equal to 41 days of amenorrhea (DA) (1), when it is given at the dose of 600 mg orally in a single administration. Past that date, the efficacy of the product alone diminishes rapidly (drop of about 10% in the success rate per week of additional amenorrhea). Swedish (2), Scottish (3) and French (4-5) studies have shown that combining Mifepristone with a synthetic prostaglandin analog (Sulprostone or Gemeprost), completely interrupts the pregnancy in 95% of the cases, for amenorrhea up to 49. These studies also indicate that combining Mifepristone with prostaglandin lowers the useful doses of prostaglandin (0.25 mg for Sulprostone, 0.5 or 1.0 mg for Gemeprost), hence a reduction in their side effects.

The optimum time period between the administration of Mifepristone and the administration of prostaglandin is 36 to 48 hours. In fact, the cervical dilation caused by mifepristone is greater at 48 than at 24 hours, and the sensitivity of uterine muscle to the contractive effect of prostaglandins is maximum 36 to 48 hours after the administration of mifepristone (6.7).

Mifepristone has been registered in France as a medical alternative to uterine aspiration of pregnancy of no more than 49 days of amenorrhea; it is prescribed at the dose of 600 mg (three 200 mg tablets) in a single administration and is followed 36 to 48 hours later by the administration of 1 mg of Gemeprost [redacted] or 0.25 mg of sulprostone

In one study of approximately 16,000 women (8), the safety for this method of interrupting pregnancy was acceptable. Within 4 hours following the administration of prostaglandin, painful uterine contractions occurred in approximately 80% of the women; these contractions necessitated treatment in 20% to 60% of the patients depending on the prostaglandin dose used (1 mg of gemeprost, 0.25 or 0.5 mg of sulprostone). During that same period, vomiting (15% of cases) and diarrhea (7.5% of cases) were observed. Faintness as a result of hypotension or lipothymia were also reported in approximately 1% of the cases.

[redacted]

Uterine bleeding necessitated a hemostatic endo-uterine procedure in 0.8% of the cases, and a transfusion in 0.1% of the cases.

Out of all the women who have used this method (approximately 60,000), three severe adverse effects of the myocardial infarction type have been reported, one of which was fatal. These infarctions seem to be connected with a coronary spasm and all of them occurred within 4 hours following the injection of sulprostone. The patients involved were all over 30 years of age and smoked. These coronary spasms are probably attributed to sulprostone and have also been described after isolated injection of sulprostone (9).

In view of these accidents, the decision was made to determine whether prostaglandins other than the ones previously studied could be combined with mifepristone.

Misoprostol is a synthetic derivative of the PGE_1 series (15-desoxy 16-hydroxy 16 methyl analog) administered orally at the dose of four 0.2 mg tablets 4 per day to treat ulcerous duodenal or gastric lesions (10).

This product is widely prescribed. At the dose of four 200 mg tablets per day, it causes no hypotension and its cardiovascular safety seems acceptable. No serious cardiovascular effect has been published to date, and the Surveillance data are favorable (11).

This prostaglandin can stimulate the contraction of smooth muscle fibers, particularly uterine fibers. It is therefore contraindicated in its current indication in pregnant women or sexually active women who do not have an effective method of contraception.

One preliminary study in 100 women (12) has shown that prescribing 600 mg of mifepristone, followed 48 hours later by 2 tablets of misoprostol, enabled interruption and complete expulsion of 95% of pregnancies of no more than 49 days of amenorrhea. The method's safety was satisfactory. The main adverse effects were nausea (35 cases), vomiting (11 cases) and diarrhea (7 cases), which symptoms did not necessitate any treatment. Conversely, the intensity of the uterine pain seems to be definitely lower than with the prior prostaglandins used (sulprostone, gemeprost). The duration of bleeding did not change.

Therefore, considering all the above information, it seems worthwhile to confirm the efficacy and safety of this combination in a large-scale study.

2. PURPOSE OF THE STUDY

The purpose of this study is to evaluate the efficacy and safety of using Mifepristone (600 mg), in combination with two 0.2 mg tablets of misoprostol administered 48 hours later, for interruption of pregnancy aged less than or equal to 49 days of amenorrhea, within the framework of the law on voluntary interruption of pregnancy in France.

3. DESCRIPTION OF THE STUDY

This is an open, multicenter trial studying the following therapeutic plan:

- Mifepristone will be administered at the dose of 600 mg (three 200 mg tablets) in the presence of the researcher on day 1 after verification of the inclusion criteria.
- Misoprostol (two 0.2 mg tablets in a single administration) will be administered 48 hours later, the morning of day 3, also in the presence of the investigator. The women will be kept under observation in a hospital setting for 4 hours.

The efficacy and safety of the treatment will be evaluated 8 to 15 days after the administration of mifepristone in a follow-up visit.

4. CHOICE OF SUBJECTS

4.1 Number

The anticipated number of patients is 500. These patients will be recruited in 24 centers.

4.2 Inclusion Criteria

The following will qualify for inclusion: women who

- request interruption of pregnancy (I.V.G.*),
- meet the mandatory statutory requirements for I.V.G. in France,
- range in age from 18 (legal age of consent; underage women can be included only with the consent of their legal guardian) to 35 years of age,
- agree to submit to the constraints of the study, specifically the follow-up visit following administration of the treatment,
- are informed of the usual procedure for a miscarriage,
- agree to undergo an surgical interruption of pregnancy should the treatment fail,
- are informed of the procedure of the study and have given their written consent to participate in it (appendix 1),

and whose pregnancy is:

- intra-uterine,
- ongoing,
- of stated age less than or equal to 49 days of amenorrhea (calculated from the first day of the last menstruation).

(The occurrence of an IUD pregnancy is not a contraindication, provided that it is removed when mifepristone is administered).

4.3. Exclusion Criteria

The following will not qualify for inclusion: women who

- have signs of spontaneous miscarriage in progress,
- have a suspicion of extra-uterine pregnancy,

*[interruption volontaire de grossesse = voluntary interruption of pregnancy]

- whose amenorrhea is longer than 49 days,
- are more than 35 years of age,
- are smokers, defined as smoking at least 10 cigarettes per day for 2 years preceding the start of the study,
- have one of the following pathologies: cardiovascular history (angina pectoris, rhythm disorders, cardiac insufficiency, severe hypertension...), asthma, glaucoma or high intraocular pressure, diabetes, hyperlipemia.
- have renal, adrenal or hepatic insufficiency currently or in their histories,
- have been treated with corticoids chronically for the preceding six months,
- have a known allergy to mifepristone,
- have anemia,
- refuse to give their written consent to participate,
- who are thought to be prone to stray from the requirements of the protocol, or who live far from the center.

5. TREATMENT

5.1 Mifepristone

The Mifepristone will be supplied by the Roussel Laboratories in the form of 200 mg tablets of micronized active product. The tablets will be packed in 3-tablet blisters.

The product will be given in a single 3-tablet administration, in the presence of the invesitgator, on an empty stomach.

The boxes of mifepristone will be labeled as follows:

- Protocol number FFR 91/486/14
- Mifepristone - Misoprostol Study
- Roussel Laboratories
- Batch No. - Expiration date
- Patient No. (0001 to 0500)

All boxes of mifepristone needed by a center will be given to that center's head pharmacist, who will distribute them to the investigator.

After verifying the inclusion and exclusion criteria, the women will be assigned a study admission number and she will then be given the box bearing that number. The numbers will be assigned in order.

A record sheet of products under study must be kept up to date by the investigator.

At the end of the study, all unused products and the product record sheet must be collected by the clinical research assistant.

5.2. Prostaglandin Analog

The prostaglandin analog used will be misoprostol (Cytotec®). It will be administered 48 hours after the administration of mifepristone at the dose of two 0.2 mg tablets in a single administration, in the investigator's presence. The women will then be observed at the center for 4 hours.

The misoprostol will be supplied to the center's head physician by the Roussel Laboratories.

5.3 Combined Treatments

5.3.1 Authorized treatments

Insofar as possible, no other treatment will be combined. If a prescription is made, the type and dose of the medication will be indicated in the observation notebook.

Treatments in progress will be indicated in the observation notebook.

5.3.2 Prohibited Treatments

- Acetylsalicylic acid and derivatives thereof, steroidal or non-steroidal anti-inflammatories, prostaglandin synthesis-inhibiting medications (if necessary, an analgesic will be used that belongs to another pharmacological class or an antispasmodic in preference over one of these medications), enzyme-inducing medications.

- oxytocics or prostaglandins other than the one used in the study.

- The patient must refrain from self-medication.

- The patient must abstain from smoking or drinking alcohol during the 48 hours between the administration of mifepristone and misoprostol, and on the day the misoprostol is administered.

6. EVALUATION CRITERIA

6.1 Efficacy

Efficacy will be evaluated 8 to 15 days after administration of Mifepristone (day 8 - day 15) by the investigator, on clinical data (occurrence of bleeding, expulsion of ovular sac, persistence of bleeding), biological and/or ultrasound data.

A distinction will be made between:

1) Interruption and complete expulsion of pregnancy (disappearance of clinical signs, drop in beta HCG compared to day 1 and/or uterine vacuity, with no need for an additional surgical procedure (aside from possible forceps-aided extraction of ovular fragments protruding from the external orifice of the cervix). The date and time of the expulsion will be noted, if possible. This will be considered as a success.

2) Interruption of pregnancy without complete expulsion.

3) Persistent pregnancy.

4) The need for a hemostatic endo-uterine procedure.

Cases 2, 3 and 4 will be followed by additional surgical therapy, the date of which will be recorded. They will be considered failures.

6.2 Safety

6.2.1. When misoprostol is administered (day 3):

Safety will be evaluated on:

- Any adverse effect occurring between day 1 (administration of mifepristone) and day 3.
- Occurrence, within 4 hours of administering misoprostol, of painful uterine contractions and digestive problems: nausea, vomiting, diarrhea. The intensity of these symptoms will be noted along with any need for a symptomatic treatment.
- For 4 hours following administration of misoprostol, hourly observation of blood pressure (systolic and diastolic) and heart rate.
- Occurrence of an adverse effect other than the ones indicated above.

6.2.2 At Follow-Up Visit (day 8 - day 15):

Safety will be evaluated based upon:

- The duration of uterine bleeding and the need for special measurements: measurement of hemoglobin concentration, medication treatment, blood transfusion, hemostatic surgical procedure.

- Any unusal clinical sign or symptom that has occured since day 3.

6.2.3 Biological Safety

This will be evaluated based upon the hemoglobin rate measured on day 1 (before administering mifepristone) and on day 8 - day 15 at the time of the follow-up visit.

7.1 Initial Evaluation (day 1)

Verify that the patient has taken the legal measures to request a voluntary interruption of pregnancy and has met the conditions stipulated by the law (waiting period):

- Record:

· the main history,
· any treatments in progress and the reasons for them,
· the date of the last menstruation.

- Verify that the age of the pregnancy is less than or equal to 49 days of amenorrhea.

- Measure the bHCG and do a uterine ultrasound.

- Determine the Rhesus group if the patient has no group card, and measure the hemoglobin rate.

- Give the patient a data sheet on the study and obtain her written consent to participate in it.

- Assign the women a study admission number and give her the 3 tablets of mifepristone contained in the box bearing that number. The treatment will be taken immediately in the presence of the investigator. The number will be noted in the observation notebook.

- Inform the women that she must refrain from smoking and drinking alcohol for the next 48 hours and on day 3.

- Make an appointment for the morning two days later (day 3).

7.2. Day 3: Administration of Misoprostol:

- Clinical examination

- Look for any adverse effect.

- Give an injection of anti D gamma globulins if the patient is Rhesus negative.

- Administer two 0.2 mg tablets of misoprostol in a single administration (if expulsion has not already occurred) in the investigator's presence.

- The patient must remain under observation at the center for the next 4 hours.

- During these 4 hours of observation, the following parameters are evaluated:

· Painful uterine contractions, nausea, vomiting, diarrhea, using the following scale:

1: minimal
2: moderate
3: major, not necessitating treatment
4: major, necessitating treatment

* the overall intensity of the pain during this observation will also be evaluated on an analogous visual scale 4 hours after administration of misoprostol,

* if a premedication is given, it will be noted in the observation notebook,

* the treatments administered will be recorded in the observation notebook.

· Heart rate, systolic and diastolic blood pressure will be measured every hour.

- Note the time of ovular expulsion if it occurs during the time that the patient is under observation.

- If the patient has chest pains, a rhythm disorder or hypotension, an EKG must be done. In the event of severe pain, rapid-acting nitrate derivatives will be prescribed, in the hypothesis of a coronary spasm.

- After 4 hours, the woman is authorized to leave the center and is given an appointment for day 8 - day 15, with a prescription for a hemoglobin measurement just before the next visit.

- An oral contraceptive to be started 24 to 48 hours later can be prescribed during this visit.

7.3. Day 8 - Day 15: Follow-up Visit:

- New clinical examination and evaluation of safety by the investigator.

- If possible note the date of ovular expulsion and the time of expulsion with respect to the time of administration of prostaglandin.

- Final evaluation of efficacy of treatment (by the data from the clinical examination, ßHCG and/or ultrasound).

- If the patient has started an oral contraceptive before this follow-up visit, note the name of the contraceptive prescribed.

- Evaluation of metrorrhagia:
  - · duration,
  - · was there any need for an emergency measurement of the hemoglobin concentration (note the result)?
  - · was there any need for a treatment (medication, transfusion, hemostatic surgical procedure)?

- In the event of failure (ongoing pregnancy, incomplete expulsion), recommend an additional surgical procedure.

- Note the results of the hemoglobin measurement.

8. DATA COLLECTION AND ANALYSIS

8.1. Data collection:

An observation notebook will be filled out for each patient admitted to the study. Only the investigator and his/her colleagues are authorized to fill in the notebook or make any corrections in it.

Any correction in the observation notebook must be made by drawing a line through the incorrect data so that it remains visible, and putting the correct data alongside it. The person who made this correction must enter the date and put his/her initials in the margin. Each observation notebook must be signed and dated by the investigator.

8.2. Data analysis:

The data will be analyzed by the Biometry Department of the Roussel Laboratories. It will be primarily descriptive.

9. AMENDMENTS TO THE PROTOCOL

There can be no modifications in the protocol without Roussel's written consent.

Any modification must be the subject of an amendment documented and justified in writing. It must be signed by the investigator accepting the change in the study procedure.

This amendment in the protocol must be submitted and approved by the Ethics Committee if it is liable to modify the expected medical benefit/risk ratio for the patient, in a way unfavorable to the patient.

If the modification of the protocol is necessary immediately to assure patient safety, the persons in charge of the study will submit the amendment to the Ethics Committee after it is applied, but as soon as possible.

10. SIDE EFFECTS AND ADVERSE EVENTS

10.1. Serious Adverse Event:

A serious adverse event is defined as:

- any event entailing a fatality or undermining the life prognosis,

- any event leaving sequelae or developing in a chronic fashion,

- any event necessitating hospitalization or extension of hospitalization,

- discovery of a congenital anomaly or a cancer.

- an overdosage.

Any serious adverse event must be immediately reported to the Roussel laboratories:

- Dr. Remi Peyron — Tel. 1 40 62 41 40, Fax. 1 40 62 49 68

OR

- Dr. Louise Silvestre — Tel. 1 48 91 46 60, Fax. 1 48 91 49 49

[redacted]

A written confirmation must be sent in the form of the adverse effect record sheet (an example is in appendix 2) either by fax or by express mail.

10.2 Benign adverse events.

These will only be reported in the case report form.

11. PATIENTS LOST TO FOLLOW-UP AND DISCONTINUED FROM THE TRIAL

Each patient entered in the study will be analyzed for safety. Only those women who have completed the trial will be able to be analyzed for efficacy.

12. NOTIFICATION OF AUTHORITIES

The Minister of Health will be informed of the study.

13. ETHICS

This study will be conducted according to the principles of the Declaration of Helsinki (see Appendix 3) and according to French laws governing clinical trials.

13.1 Consent

Before inclusion of a patient in the study, her written consent will be obtained (signed by the patient and preceded by the statement "read and approved".) In order to obtain her consent, she will be provided with a document containing information on the study in which she has been asked to take part.

In addition, the investigator will sign an "identification and obtaining of consent" form, "thus attesting that the patient's consent has indeed been obtained".

13.2 Ethical Committee:

The protocol will be submitted to an Ethical Committee.

The study will begin only after Roussel Laboratories has received a copy of the committee's written agreement.

In the case of a protocol amendment, this amendment will have to be submitted to and approved by the Ethical Committee, if it is likely to alter the relationship between the patients' medical benefit and risks in an unfavorable manner.

14. CONFIDENTIALITY

The data collected during this study will be considered confidential.

The information provided by Roussel Laboratories (product brochure, protocol, case report form) are likewise confidential.

For each patient, the data will be identified by the patient's number in the study and by her initials, and will be processed anonymously in the analyses.

All the data on this study must be kept available to the other investigators participating in it, the Roussel Laboratories Coordinator, the Quality Control Officer, the Ethics Committee, and the Overseeing Authorities.

15. STUDY FOLLOW-UP AND QUALITY CONTROL

The members of the Roussel Laboratory will be in regular contact with the investigator by on-site visits and telephone calls to monitor the progress of the study and make sure that it is conducted pursuant to the protocol.

The observation notebooks will be reviewed in detail during each visit.

The investigator and his/her team agree to cooperate with the monitor, and specifically to furnish any missing documents and information whenever possible.

Each observation notebook will be signed by the investigator, who must initial and date all corrections.

If data is missing or unavailable, the reason will be stated.

The participation in this study means that the investigator accepts the possibility of a quality control audit to verify that the procedures described in the protocol have been followed throughout the study.

16. DURATION OF STUDY

The study will start in June 1991 and will last about 3 months.

17. INSURANCE

The investigator's civil liability, under this study, is covered by insurance purchased by the Roussel Laboratories (appendix 4).

18. PUBLICATION

Any presentation or publication of the results of this study must first be the subject of an agreement between the investigators and the Roussel Laboratories.

19. INVESTIGATOR'S LIABILITY AND UNDERTAKING

All the information on the product tested and the results of the study are considered to be confidential.

I have read the protocol and I feel that it contains all the information necessary for conducting the trial.

I undertake to conduct this trial pursuant to the protocol; I will not make any modification to to the trial without the written agreement of the Roussel Laboratories.

I undertake not to start the study until an Ethics Committee has given its agreement.

I will conduct this trial according to the principles set forth in the Helsinki Statement, and in conformity with Good Clinical Practice; specifically, I will obtain the informed consent of each patient before they enter the study.

I further undertake to carefully fill in the observation notebooks, to respect the procedure in the event of serious side effect and to monitor the management of the product under experimentation.

I agree to the monitoring of the study by a member of Roussel Laboratories and to the outcome of a quality control audit.

I will keep all information directly concerning the study available to the Roussel Laboratories and the Overseeing Authorities.

I will retain the gross data collected in this study for a period of 10 years.

Product name: MIFEPRISTONE
Protocol No.: FFR/91/486/14

Date Signature of Investigator

Date Signature of Roussel Laboratories Coordinator

APPEARS THIS WAY
ON ORIGINAL

REFERENCES

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7. M.L. SWAHN, M. BYGDEMAN - The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. Br. J. Obstet. Gynaecol., 1988, 95, p. 126-134.

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10. R.L. HERTING, C.H. NISSEN - Overview of misoprostol clinical experience. Dig. Dis. Sci., 1986, 31, (supplement), p. 475-545.

11. R.A. WILDEMAN - Focus on misoprostol: Review of worldwide safety data. Clin. Invest. Med. 1987, 10, 243-245.

12. E. AUBENY, E.E. BAULIEU - Contraceptive effect of combining RU 486 with an active prostaglandin by mouth. C.R. Acad. Sci., Paris (in press).

CHECK-LIST

DAY 1: INCLUSION:

- Confirmed pregnancy, progressing normally,

- Clear request for voluntary interruption of pregnancy, legal measures taken,

- Amenorrhea less than or equal to 49 days,

- Age over 18 years (or authorization from legal guardian for minors) and less than or equal to 35 years,

- No contraindication for the method,

- Explain to the patient what happens in a miscarriage and the modalities of the protocol, and obtain her informed consent,

- Measure ßHCG and/or ultrasound,

- Measure hemoglobin, blood group,

- Administer 600 mg (three 200 mg tablets) of mifepristone in a single administration in the investigator's presence,

- Tell the patient that she must not smoke or drink alcohol for the next 48 hours and on D3.

- Appointment for D3.

DAY 3: ADMINISTRATION OF MISOPROSTOL:

- Injection of anti D gamma globulins if the patient is Rhesus negative,

- Note any functional signs that appear after administration of Mifepristone,

- Verify that expulsion did not occur between D1 and D3,

- If no expulsion has occurred, administer misoprostol: two 0.2 mg tablets in a single administration,

- Observance for 4 hours following that administration:

  · Every hour measure the heart rate, systolic and diastolic blood pressure,

  · Watch for any painful uterine contractions, nausea, vomiting, diarrhea, evaluate their intensity and record any treatments administered,

- Appointment for day 8 - day 15, with prescription for hemoglobin measurement just before the next visit.

CHECK-LIST

- Possible prescription of an oral contraception to be started 24 to 48 hours later.

DAY 8 - DAY 15: FOLLOW-UP VISIT:

- Evaluate the efficacy and safety of the treatment,

- If possible, note the date and time of ovular expulsion,

- Note the results of the hemoglobin measurement.

- In the event of failure (ongoing pregnancy or uterine retention), recommend an additional surgical procedure.

APPEARS THIS WAY

APPENDIX 1

- Information form intended for patient.

- Written consent form.

APPENDIX 1

READ THIS SHEET CAREFULLY AND HAVE THE PHYSICIAN EXPLAIN THE POINTS THAT DO NOT SEEM CLEAR TO YOU.

BEFORE TAKING MIFEGYNE, THE PHYSICIAN WILL HAVE YOU SIGN A FORM CERTIFYING THAT YOU HAVE READ AND UNDERSTOOD THIS SHEET.

INFORMATION FOR PATIENTS

You have requested an interruption of pregnancy. You are asked to participate in a study to evaluate, on a wide scale, the efficacy of combining Mifegyne and an oral prostaglandin, misoprostol, in the voluntary interruption of pregnancy.

This study respects the laws on clinical trials and the principles of the Helsinki statement: it has been submitted to the Ethics Committee of Broussais Hospital, which issued a favorable opinion on June 4, 1991.

A preliminary study was done on 100 women and showed that this method seems to be as effective as the method currently used, which combines Mifegyne with a prostaglandin ——————————————. It is necessary to confirm these results on a wider scale and five hundred women will participate in this study. They will be recruited at 24 public or private hospital centers.

Mifegyne is a medication that blocks the effect of progesterone, the hormone that maintains pregnancy. However, its effect needs to be supplemented, 36 to 48 hours later, by the effect of a prostaglandin, a substance that increases uterine contractions.

Mifegyne can be used only in compliance with current regulations regarding voluntary interruption of pregnancy (laws of 1975 and 1979).

The three Mifegyne tablets must be taken less than 49 days after the first day of your last menstruation.

Mifegyne must not be used in the following cases:

- if the pregnancy has not been confirmed,
- if extra-uterine pregnancy is suspected,
- if the first day of your last menstruation was more than 50 days ago,
- if you are more than 35 years of age,
- in the event of the following diseases: renal insufficiency, hepatic insufficiency, adrenal insufficiency, blood coagulation anomaly or administration of anticoagulant medication, anemia, asthma or history of asthma, cardiovascular history (angina pectoris, rhythm disorders, cardiac insufficiency, severe hypertension...), diabetes, hyperlipemia, glaucoma or high intraocular pressure,
- in the event of prolonged treatment by corticoids,
- if you are a smoker (at least 10 cigarettes per day for the last 2 years).

INTERRUPTION OF PREGNANCY BY MIFEGYNE HAS LIMITS AND INVOLVES CONSTRAINTS THAT YOU MUST BE FAMILIAR WITH

1. The administration of Mifegyne must be followed 36 to 48 hours later by the administration of a prostaglandin, to obtain maximum efficacy of the method.

2. Mifegyne is not 100% effective, and you yourself will not be able to judge the efficacy of the method. In fact, the uterine bleeding that will occur is not proof of efficacy, and expulsion of the egg, which often occurs a few hours after the prostaglandin is administered, may be incomplete.

You must therefore undergo a mandatory follow-up visit, 12 to 15 days after the Mifegyne is administered, to verify that your pregnancy has indeed been interrupted.

In the event of failure, the interruption of pregnancy or evacuation of the placenta debris can be done only by surgical means.

3. As in any interruption of pregnancy, uterine bleeding (metrorrhagia) occurs in nearly all cases. It is sometimes very copious, and may then necessitate emergency treatment. Therefore, you must remain near the prescribing center until the follow-up consultation, and the doctor will tell you where to telephone and where to go if necessary.

4. Abdominal pains justifying treatment, nausea, vomiting, diarrhea and feeling faint, occur in some cases after administration of the prostaglandin. Therefore, it must be followed by several hours of observation at the prescribing center.

5. THE FOLLOW-UP CONSULTATION IS FOR VERIFYING THAT THE PREGNANCY HAS BEEN INTERRUPTED. INDEED, IF THE PREGNANCY CONTINUES AFTER THE ADMINISTRATION OF MIFEGYNE AND PROSTAGLANDIN, THE FETUS OR UNBORN CHILD COULD BE DEFORMED.

6. A new pregnancy can occur immediately after interruption of the pregnancy: if you do not wish to become pregnant again, a contraceptive must be started early.

7. If you belong to a Rhesus negative blood group, the prevention of rhesus immunization must be done.

8. Exceptional cases of cardiovascular accidents have been reported after injection of a prostaglandin. Consequently, the Mifegyne-prostaglandin analog method is contraindicated when the cardiovascular risk is high due to the following factors: smoking, hyperlipemia, diabetes, high blood pressure, cardiovascular history, being older than 35 years of age.

9. You must refrain from TOBACCO and ALCOHOL for the two days in between the administration of Mifegyne and the administration of the prostaglandin, and on the day the prostaglandin is administered.

Moreover, the study can be interrupted:

- for medical reasons at the doctor's discretion,

- of your own volition, with no explanation required of you.

At your request and under medical supervision, a uterine evacuation can then be done.

In the event of an emergency or for any question relating to this study, you can telephone:

· Dr. at number:

APPENDIX 1 (CONTINUED)

PRACTICAL DESCRIPTION OF THE METHOD

DAY OF FIRST CONSULTATION

· You request a voluntary interruption of pregnancy.

· The first day of the last menstruation was no more than 42 days ago.

· as of this day 0, you have one week in which to think it over (pursuant to the law on voluntary interruption of pregnancy).

ONE WEEK LATER - 2nd STAGE:

· You confirm your request for voluntary interruption of pregnancy.

· You have no contraindication for using Mifegyne or the prostaglandin.

· You have read the information sheet on Mifegyne, you have obtained the additional information that you have requested and you have signed the form certifying that you are informed.

· You swallow 3 tablets of Mifegyne in the doctor's presence (day 1)

· You go home with a new appointment 48 hours later, knowing where to telephone or where to go if necessary.

· Uterine bleeding usually starts one or two days later.

TWO DAYS LATER (DAY 3):

· You return to the prescribing center.

· The prostaglandin is administered (2 tablets in a single administration)

· You rest for several hours in the center, then you go home with, if applicable, a prescription for an oral contraceptive.

· The egg is expelled while you are in the center or within the next few days.

· Bleeding persists, usually until the follow-up consultation.

APPENDIX 1 (CONTINUED)

PRACTICAL DESCRIPTION OF THE METHOD

FOLLOW-UP VISIT: 5 to 13 days after the administration of prostaglandin

· You return to the prescribing center for the follow-up consultation: the doctor verifies that the expulsion is complete. If the pregnancy persists or expulsion is incomplete, the investigator will recommend a surgical technique (aspiration) to you.

WRITTEN INFORMED CONSENT

Protocol No.:

APPEARS THIS WAY ON ORIGINAL

Title of study:

I, the undersigned: _____

residing at: _____

_____

_____

do agree to participate, with full knowledge and full liberty, in the medical research conducted by Dr. _____

The medical information gathered during this study is confidential. My identity will not be revealed in any reports or publications produced by this study.

I am aware that I may refuse to participate in this research or withdraw my consent at any time, with no liability on my part.

I state that the purpose of the research, the conditions under which it will be conducted and its duration have been clearly indicated to me along with the constraints and foreseeable risks, including if the research is stopped prematurely. A summary of this information has been given to me.

Assigned
treatment number

Done in _____
On _____

Signature of subject preceded by the notation
"Read and Approved"

- The original is to be kept for at least 10 years by the investigator.

APPENDIX 2

- Serious adverse event/report form record sheet

CLINICAL TRIAL
SERIOUS ADVERSE EVENT REPORT FORM RECORD SHEET

Ø TO BE COMPLETED IN THE EVENT OF:

- adverse event undermining the life prognosis

- death

- discovery of a cancer or a congenital anomaly

- adverse event necessitating hospitalization or extension of hospitalization

- adverse event entailing sequelae or developing in a chronic fashion

- overdosage

REGARDLESS OF THE RELATIONSHIP WITH THE MEDICATION BEING STUDIED

Ø The first copy must be sent to the monitor, the second must be kept by the investigator, the third must be included in the observation notebook.

Ø Be as complete and precise as possible in describing the medical history.

If possible, attach a copy of the relevant additional tests and send a copy of the hospitalization report as soon as it is available.

CLINICAL TRIAL
SERIOUS ADVERSE EVENT REPORT FORM RECORD SHEET

PROTOCOL/INVESTIGATOR

Protocol No.:
Center No.:

Indication:

Investigator's name:

Address: Country:

PATIENT Number assigned in the study: Surveillance Number (local)

Initials Age Sex Weight Height

M F kg g m cm

Occupation: Ethnic origin:

Relevant history:

Drug intolerance: No Yes Unknown Drugs involved:

ADVERSE EVENT Onset date

D M Y

Description:

Hospitalization (or extension of hospitalization) necessary: Yes No

Treatment:

PROGRESS Complete cure Chronic or sequelae

Effect still in progress Unknown

Death

Ø Date

d m y

Ø Autopsy Yes No

Ø Cause of death

MIF 007557

CLINICAL TRIAL
SERIOUS ADVERSE EVENT REPORT FORM RECORD SHEET

PROTOCOL/INVESTIGATOR

Protocol No.:
Center No.:

Indication:

Investigator's name:

Address: Country:

PATIENT Number assigned in the study: Surveillance Number (local)

Initials Age Sex Weight Height

M F kg g m cm

Occupation: Ethnic origin:

Relevant history:

Drug intolerance: No Yes Unknown Drugs involved:

ADVERSE EVENT Onset date D M Y

Description:

Hospitalization (or extension of hospitalization) necessary: Yes No

Treatment:

PROGRESS Complete cure Chronic or sequelae

Effect still in progress Unknown

Death

Ø Date d m y

Ø Autopsy Yes No

Ø Cause of death

111

87

117

MIF 007558

CLINICAL TRIAL
SERIOUS ADVERSE EVENT REPORT FORM RECORD SHEET

PROTOCOL/INVESTIGATOR

Protocol No.:
Center No.:

Indication:

Investigator's name:

Address: Country:

PATIENT Number assigned in the study: Surveillance Number (local)

Initials Age Sex Weight Height

M F kg g m cm

Occupation: Ethnic origin:

Relevant history:

Drug intolerance: No Yes Unknown Drugs involved:

ADVERSE EVENT Onset date

D M Y

Description:

Hospitalization (or extension of hospitalization) necessary: Yes No

Treatment:

PROGRESS Complete cure Chronic or sequelae

Effect still in progress Unknown

Death

Ø Date

d m y

Ø Autopsy Yes No

Ø Cause of death

SUMMARY

(Precise description of medical history concerning the event)

SUMMARY

(Precise description of medical history concerning the event)

SUMMARY

(Precise description of medical history concerning the event)

MEDICATION STUDIED

Name _____

or

Code ☐

Administration plan:

dose ☐ units ___ frequency _____

Method of administration: _____

Treatment date:

Start: ☐☐ ☐☐ ☐☐ (D M Y)

End: ☐☐ ☐☐ ☐☐ (D M Y)

In progress ☐

Administration of medication after start of reaction:

Immediate results:

Continued same dose ☐

Interrupted ☐

Improvement ☐

No change ☐

NA* ☐

Reduced ☐

NA* ☐

Aggravation ☐

Uninterpretable ☐

Readministration:

No ☐ Yes ☐ NA* ☐

Date: ☐☐ ☐☐ ☐☐ (D M Y)

Reappearance of reaction:

No ☐ Yes ☐ NA* ☐

Uninterpretable ☐

*not applicable

CONCOMITANT MEDICATIONS

Name	Dose/ 24 hours	Start date	End date	Indication

CAUSAL RELATIONSHIP

Investigator's opinion:

ruled out ☐ improbable ☐

possible ☐ probable ☐ very probable ☐

unable to evaluate ☐

explain why: _____

This sheet was filled out:

Ø on date: ☐☐ ☐☐ ☐☐ (D M Y)

Ø name of monitor and signature

Ø by: _____ _____

Ø title: _____

Ø signature _____

MEDICATION STUDIED

Name _____

or

Code ☐

Administration plan:

dose ☐ units ____ frequency _____

Method of administration: _____

Treatment date:

Start: ☐☐☐ (D M Y)

End: ☐☐☐ (D M Y)

In progress ☐

Administration of medication after start of reaction:

Immediate results:

Continued same dose ☐

Interrupted ☐

Improvement ☐

No change ☐

NA* ☐

Reduced ☐

NA* ☐

Aggravation ☐

Uninterpretable ☐

Readministration:

No ☐ Yes ☐ NA* ☐

Date: ☐☐☐ (D M Y)

Reappearance of reaction:

No ☐ Yes ☐ NA* ☐

Uninterpretable ☐

*not applicable

CONCOMITANT MEDICATIONS

Name	Dose/ 24 hours	Start date	End date	Indication

CAUSAL RELATIONSHIP

Investigator's opinion:

ruled out ☐ improbable ☐

possible ☐ probable ☐ very probable ☐

unable to evaluate ☐

explain why: _____

This sheet was filled out:

Ø on date: ☐☐☐ (D M Y)

Ø by: _____

Ø name of monitor and signature _____

Ø title: _____

Ø signature _____

MIF 007564

MEDICATION STUDIED

Name _____

or

Code ☐

Administration plan:

dose ☐ units ____ frequency _____

Method of administration: _____

Treatment date:

Start: ☐☐☐ (D M Y)

End: ☐☐☐ (D M Y)

In progress ☐

Administration of medication after start of reaction:

Continued same dose ☐

Interrupted ☐

Reduced ☐

NA* ☐

Immediate results:

Improvement ☐

No change ☐

Aggravation ☐

Uninterpretable ☐

NA* ☐

Readministration:

No ☐ Yes ☐ NA* ☐

Date: ☐☐☐ (D M Y)

Reappearance of reaction:

No ☐ Yes ☐ NA* ☐

Uninterpretable ☐

*not applicable

CONCOMITANT MEDICATIONS

Name	Dose/ 24 hours	Start date	End date	Indication

CAUSAL RELATIONSHIP

Investigator's opinion:

ruled out ☐ improbable ☐

possible ☐ probable ☐ very probable ☐

unable to evaluate ☐

explain why: _____

This sheet was filled out:

Ø on date: ☐☐☐ (D M Y)

Ø by: _____

Ø name of monitor and signature _____

Ø title: _____

Ø signature _____

APPENDIX 3

DECLARATION OF HELSINKI

MIF 007566

[pages 119-123 contain a French translation of the Helsinki Declaration, originally written in English]

Declaration of Helsinki

Recommendations guiding medical doctors in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964
and As Revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.

Introduction

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the world, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

123A
97

APPENDIX 4

Insurance

CERTIFICATE OF INSURANCE
OF PROFESSIONAL CIVIL LIABILITY OF PERSONS INDICATED
in Law N° 88.1138 of December 20, 1988 amended

certifies that the contract signed by ROUSSEL UCLAF, 35 Boulevard des Invalides - 75007 Paris, under N° covers the civil liability of:

ROUSSEL LABORATORIES
97 Rue de Vaugirard
75006 Paris

in their capacity as promoter of biomedical research, and the civil liability of any person involved, pursuant to Article L.209.7 of the Public Health Code, in the research entitled:

"Efficacy and safety of mifepristone (RU 486) at the dose of 600 mg in a single administration in combination with misoprostol as an alternative to uterine aspiration for interruption of pregnancy aged less than or equal to 49 days of amenorrhea"

This contract includes the coverage pursuant to Decree 91.440 of May 14, 1991.

This certificate implies only a presumption of coverage undertaken by the Insurer.

Paris, June 21, 1991
To be valid for all lawful purposes

FOR THE COMPANY:

MIF 007570

PUBLIC ASSISTANCE - PARIS HOSPITALS

BROUSSAIS HOSPITAL

Dr. Rémi Peyron
Laboratoires Roussel
97, rue de Vaugirard
75279 PARIS CEDEX 06

Paris, October 30, 1991

Sir,

You have informed me of the favorable results of the study of misoprostol associated with mifépristone as an alternative to aspiration for voluntary interruption of pregnancy with a gestational age lower than or equal to 49 days of amenorrhea in 387 women.

The study you are conducting had received the approval of the Local Ethics Committee of the Broussais Hospital (protocol No 229 {meeting No 60} dated June 4, 1991 as a follow-up to protocol 209 approved on 12/18/90 {meeting No 55} and amended on 03/26/91 {meeting No 58}). The study will be conducted in 22 centers in an expected number of 500 women

In view of the preliminary results and in accord with Dr. AUBENY, coordinator, you wish to continue the same protocol in 25 centers in 500 other volunteers in order to attain the number of 1000 cases required by the Commission for Marketing Authorization.

Moreover, you wish to continue the study with a simplified case report form upon completion of the 1000 cases until approval of the use of misoprostol in association with mifépristone by the Commission for Marketing Authorization.

These amendments do not seem to pose a problem. I even believe it would be prejudicial, in view of the body of knowledge available, to stop or postpone this study or to ask the investigators to return to the use of sulprostone or géméprost whose untoward effects are known.

Unfortunately, the Local Ethics Committee of which I was secretary, has discontinued its work and an Advisory Committee for the Protection of Human Subjects in Biomedical Research has not yet been established at the Broussais Hospital. You will have to seek the advice of the newly established committee. I shall be at their disposal for any information they might need.

Sincerely yours

Laboratoires ROUSSEL
Medical Department

October 1991

AMENDMENT TO PROTOCOL FFR/91/486/14
(Compared to the May 1991 version)

Efficacy and tolerance of mifépristone (RU 486) at the dose of 600 mg in a single administration in association with misoprostol as an alternative to uterine aspiration in the interruption of pregnancy with a gestational age lower than or equal to 49 days of amenorrhea.

⇒ **NUMBER OF SUBJECTS**

Page 3, paragraph 4.1 the anticipated number of patients is 1000 instead of 500.

⇒ **EXTENSION OF THE STUDY**

Upon completion of the study with the anticipated 1000 subjects, the centers that so wish may continue the study. The extension study will follow the same protocol, except for the following points :

- the number of subjects will not be defined, the study will be discontinued as soon as the marketing authorization is obtained for the association mifépristone-misoprostol.
- elimination of hemoglobin determination on Day 1 and Day 8 - Day 15 (paragraph 6.2.3, page 7 deleted).
- a simplified case report form will be filled out for each patient.

DATE :

For the Investigator	For the Sponsor
Dr. V. TARGOSZ	Dr. R. PEYRON

COPY TO BE SIGNED AND RETURNED TO LABORATOIRES ROUSSEL

APPENDIX 10.3.1.

CLINICAL TRIALS IN PROGRESS

ORIGINAL
ORIG AMENDMENT

The Danco Group

bc

Reviewed
See Chem. Rev.
#3.

August 13, 1999

2/19/00

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
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 032 - Chemistry, Manufacturing and Controls (CMC) Section II for Drug Product

Dear

This Amendment 032 is the complete CMC section for our Drug Product.

As agreed during our April 9, 1999 meeting with the FDA, we are filing the CMC section with one-month room temperature stability data and one month accelerated stability data. We will provide three months room temperature and three months accelerated stability data in October. We request that the FDA initiate review of this CMC submission as soon as possible.

Under separate cover a copy of this CMC section has been sent to the attention of U.S. Food and Drug Administration District Office.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely,

1S

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

3. Specifications and Analytical Methods for Inactive Ingredients

3. Specifications and analytical methods for inactive ingredients

3.1 Controls for all inactive ingredients

All inactive ingredients, listed below, are quality controlled by using USP 23/NF 18 specifications and analytical methods instead of the EP specifications and analytical methods used previously.

No non-compendial inactive ingredients are used in mifepristone tablets.

Please refer to USP 23/NF 18 for specifications and analytical methods for all the inactive components. The copies of the analysis reports provided by and the vendor's certificates of analysis for all the inactive ingredients listed below are attached in this section.

- Colloidal silicon dioxide, anhydrous
- Corn starch
- Povidone
- Cellulose microcrystalline
- Magnesium stearate
-
-

APPEARS THIS WAY
ON ORIGINAL

THIS PAGE IS INTENTIONALLY BLANK

MIF 007577

The Danco Group

August 30, 1999

ORIGINAL
NEW CORRESP
NC

Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

noted
2/19/00

SEP 2 1999
HFD-580

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

Dear

We wish to confirm that the drug product manufacturer referred to in Amendment 032 of our NDA, will carry out the drug product manufacturing including the final commercial product packaging.

Sincerely,

Draft
2/8/00

Enclosure

CC:

Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

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

Doc1096

MIF 007578

Population Council

ORIGINAL

NEW CORRESP

NC

September 3, 1999

VIA FEDERAL EXPRESS

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

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

Enclosed please find five (5) copies of Volume 1.1 of our NDA 20-687.

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

Enclosures

cc: Sandra P. Arnold

FHS:as

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MF'AO

CSO INITIALS

DATE 9/9

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

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	September 13, 1999
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-Dimethylaminophenyl]-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) ☐ 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

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 007580

ORIGINAL

ORIG AMENDMENT

The Danco Group

September 13, 1999

Reviewed See Chem Rev #3. 2/19/00

SEP 14 1999 HFD-580

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
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 034 - Use of Roussel Uclaf as Reference Standard for Drug Substance

Dear

This Amendment 034 confirms that Danco is utilizing the Roussel Uclaf (not the Gedeon Richter) drug substance and process as the reference standard for manufacture of mifepristone drug substance by the Shanghai HuaLian Pharmaceutical Co., Ltd. All references used and comparisons made in Amendment 025 (CMC for Drug Substance) and Amendment 028 (Supplement to CMC for Drug Substance) are to Roussel Uclaf and not Gedeon Richter.

Please don't hesitate to contact me if you have any questions on this Amendment 034.

Sincerely,

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

Enclosure

cc:

Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ MEMO
DATE

MIF 007581

Population Council

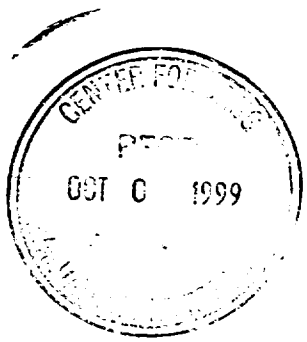
ORIGINAL

ORIG AMENDMENT

BL

September 30, 1999

VIA FEDERAL EXPRESS



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

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

Dear

As a follow-up to Dr. Shelley Clark's letter of September 8, 1999, regarding foreign labeling for mifepristone, we are enclosing copies of the following current labels as received from Exelgyn, the French Company:

Appendix 1: Product License and Labeling for France, United Kingdom and Sweden

Appendix 2: Patient Information Leaflets

a. France
b. United Kingdom
   (1) Therapeutic termination of pregnancy between 13 and 20 weeks gestation
   (2) Surgical termination of pregnancy
   (3) Medical termination of pregnancy of up to 63 days gestation
c. Switzerland
d. (Sweden does not require patient leaflets for hospital products.)

Appendix 3: Original English version of European Patient's Information Leaflet translated into various languages

Appendix 4: European Summary of Product Characteristics, 6 July 1999, with cover letter of approval under the Mutual Recognition Procedures of the European Union.

Appendix 5: Copies of box labeling for France and the United Kingdom

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

We have enclosed three (3) sets of the above labels. Please let us know if you need any additional sets of labels.

Sincerely yours,

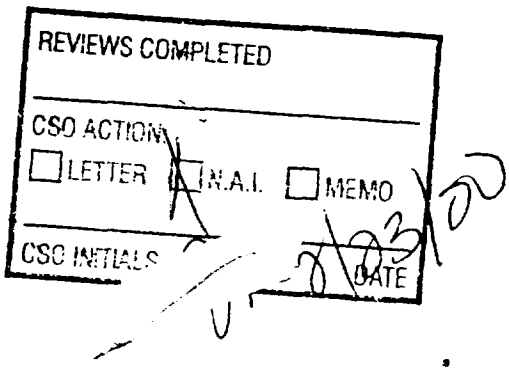
Frederick A. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

Enclosures

cc: Sandra P. Arnold
Shelley Clark

FHS: lm



APPEARS THIS WAY
ON ORIGINAL

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

ORIGINAL

ORIG AMENDMENT

BM

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

10/7/99

October 5 1999

VIA FEDERAL EXPRESS

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

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

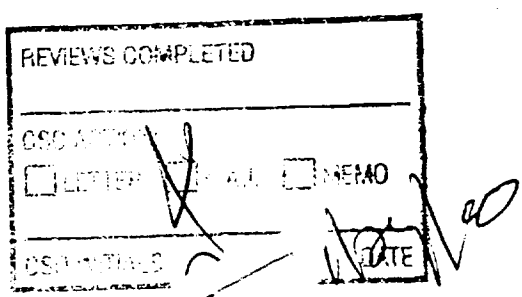
Dear Ms.

Enclosed please find answers to the questions raised by . We have answered all of s questions except for the one concerning the number of subjects who had surgery for excessive, prolonged bleeding. We will provide the answer to this last question as soon as possible.

Please let us know if you need any additional information.

Very truly yours,

Sandra Arnold



Enclosures

cc: Shelly Clark

Dr. Frederick Schmidt
Dr. Beverly Winikoff

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: samold@popcouncil.org http://www.popcouncil.org

1. **Question:**

Beverly Winikoff's presentation to the Advisory Committee referred to:

26 hospitalizations
41 hemorrhages
32 surgical interventions for bleeding

Are these numbers correct? Where are they shown in the integrated summary of the trial?

Answer:

According to our notes from the Advisory Committee meeting, this information was presented by Dr. Ann Robbins, not Dr. Beverly Winikoff, during the report on the safety of mifepristone plus misoprostol for medical abortion. In Dr. Robbins' presentation, the number of hospitalizations (26) in the U.S. Trials refers to the number of visits to the hospital and to the emergency room that were considered to be study drug related. Under section 6.7 "death, other serious and potentially serious adverse events" of the combined summary of safety for mifepristone, we document that there were eight (8) hospital visits and eighteen (18) emergency room visits that could have been drug related.

At the time of Dr. Robbins presentation to the Advisory Committee, the data from the U.S. Trials of Mifepristone presented to the Advisory Committee were considered preliminary and were in the process of being analyzed. The correct number of hemorrhages and surgical interventions are reported in the combined summary of safety for mifepristone (99 cases of medical intervention for bleeding (Table 9.2), 9 cases of severe uterine hemorrhage related to mifepristone (Table 4.1), and 127 cases of severe uterine hemorrhage related to misoprostol (Table 4.2)). If you are interested, we would be glad to send you a more complete explanation of the discrepancies between the numbers in Dr. Robbins' presentation and the numbers in the combined summary, as soon as we have identified the precise definitions and data used to calculate the numbers for the presentation to the Advisory Committee.

2. **Question:**

Wayne Bardin's presentation at the Advisory Committee referred to:

21 hospitalizations for severe bleeding
15 patients with surgery for severe bleeding

Where are each of these reflected in the integrated summary of the trial?

Answer:

Dr. Bardin presented data only from the two (2) French Pivotal Clinical Trials at the Advisory Committee. These clinical results are included in the Integrated Summary of Safety Information, Volume 1.89, NDA 20-687, March 14, 1996.

A clarification of the number of patients who were hospitalized for severe bleeding and treated surgically for severe bleeding in the two (2) French Pivotal Clinical Trials is presented below:

Hospitalizations: A total of 21 patients were hospitalized in the two (2) French Pivotal Clinical Trials due to an adverse event (Table 4.17, page 167). Eight (8) of these patients were women who were hospitalized for metrorrhagia or excessive bleeding (pages 93 and 167). The reason for hospitalizations in the remaining 13 patients are also given in Table 4.17, page 167.

Surgical Treatment for Severe Bleeding: In the two (2) French Pivotal Studies, metrorrhagia or excessive bleeding was reported in 52 patients and was reported as severe in 21 patients (page 93 and Table 4.14, page 164). Seven (7) of the 21 patients with severe metrorrhagia were treated surgically (Table 4.19, page 94). The treatments for the remaining 14 patients with severe metrorrhagia are also summaried in Table 4.19. In addition to the 21 patients treated with bleeding characterized as severe, 14 other patients were treated for bleeding or anemia (page 94 and Table 4.20, page 95). Eight (8) of these 14 patients treated for bleeding or anemia were treated surgically.

Therefore the 15 patients referred to in your question concerning the subjects who received surgery for bleeding comprised seven (7) patients in the first group with severe bleeding and the other eight (8) patients in the second group.

3. Question:

Where in the integrated summary are all serious adverse events discussed?

Answer:

French Pivotal Studies: The serious adverse events are presented in the Integrated Summary of Safety Information, Vol. 1.89, NDA 20-687, March 14, 1996, section 8.9.5.2. Adverse Events in Pivotal Clinical Trials, pages 89-97.

In addition, there were 13 patients who became lost to follow-up while the abortion process was unfinished (Vol. 21, page 19). Despite repeated attempts to contact these patients, the investigators were unable to obtain further information; therefore the ultimate pregnancy outcomes of these patients are unknown.

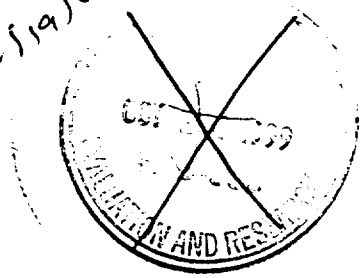
APPEARS THIS WAY
ON ORIGINAL

The Danco Group

October 26, 1999

Reviewed
See Chem Rev. #3
2/19/00

ORIG AMENDMENT
BC



Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
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 035 - Danco Produced Drug Product-3 Month Accelerated Stability Data

Dear

As a follow up to Danco's commitment to provide the FDA with three (3) month accelerated stability data from the Danco lot 99005 demonstration batch of drug product, we now enclose the data for review by your Division, along with additional supportive data to better frame the expiration period issues.

Pursuant to our prior discussions concerning Danco's efforts to replace the original drug substance and product manufacturer, Roussel Uclaf ("RU"), Danco has secured contract manufacturers who are utilizing the same RU mifepristone synthesis and tabletting processes as described in RU's original CMC submission for NDA No. 20-687. The CMC's for Danco's drug substance and drug product manufacturers have been filed as Amendments 025 and 032, respectively. The enclosed three (3) month accelerated stability data on the Danco mifepristone tablet lot 99005 continues to exhibit acceptable analytical and physical performance. Furthermore, this lot 99005 performs comparably to lots of mifepristone tablets previously manufactured by RU and used in the U.S. clinical studies.

We have enclosed applicable shelf-life and accelerated stability data on various lots of mifepristone tablets produced by both RU and Danco:

A data from the original NDA submission by the Population Council **(RU Stability Data for Mifepristone Tablets)**,

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

B data from ongoing stability studies of the RU tablet lot (JMP 25524-109) used in the original U.S. clinical studies **(Stability Data for RU Lot JMP 25524-109)**, and

C data from mifepristone tablet demonstration lot 99005 produced by Danco's contract drug product manufacturer using drug substance produced by Danco's drug substance contract manufacturer **(Stability Data for Danco Lot 99005)**.

A ***RU Stability Data For Mifepristone Tablets.*** The RU data for blister-packaged mifepristone tablets (stability lots RG 21236-12, RG 21236-44 and RG 21236-50), as originally presented in the NDA (CMC Volume 2 Section B: Drug Product, pages 473-478) are presented in **Attachment A**. The analytical data show that, when stored for sixty (60) months at room temperature (23°C), the tablets continued to perform within specification. Reported assay results fell within the specification range of 95-105% of the product label claim, with no appreciable change being observed in impurity or dissolution performance. The physical test data show that appearance, average mass, disintegration, and hardness also remained consistent throughout the sixty (60) month period. Similar acceptable analytical and physical test data also are observed when tablets are stored at 37°C or 50°C for sixty (60) months, with only minor changes in appearance and TLC assay being noted after twenty-four (24) months storage at the 50°C storage condition. All of these data demonstrate that the mifepristone tablet manufacturing process produces a robust and stable drug product.

B ***Stability Data for RU Lot JMP 25524-109.*** The Population Council, in cooperation with Danco, has continued to perform stability testing of RU tablet lot JMP 25524-109, which was manufactured in 1994 and used in the U.S. clinical studies. The data collected to date from three (3) separate stability studies conducted on this lot are presented in **Attachment B**. The first series of studies, conducted during 1994 and 1995, included two (2) studies, one controlled room temperature study for twelve (12) months, and one accelerated study (40°C) for twelve (12) months. Another controlled room temperature (25°C/60%RH) stability study which was concluded on May 12, 1999, provides additional data from 1997 to 1999. The analytical data show that assay, impurity, and tablet dissolution performance were acceptable in all three (3) studies throughout the stability test period, indicating that lot JMP 25524-109 is still maintaining acceptable analytical performance levels fifty-nine (59) months after the date of manufacture.

The tablets for each of the three (3) stability studies described above were stored under bulk storage conditions until they were placed on stability. It should also be noted that the last stability study, the eighteen (18) month controlled room temperature study, was initiated forty (40) months after the date of manufacture of lot JMP 25524-109. Thus, the data from these studies represent a worst case analysis of anticipated tablet performance. In all instances, including the final time point of the eighteen (18) month controlled room

temperature study, all data were acceptable. These stability testing data further support that the tablet manufacturing process is robust and produces a stable drug product, which could reasonably have an expiration period of thirty-six (36) months, as requested in the original NDA.

C ***Stability Data for Danco Lot 99005.*** In keeping with the stability protocol, demonstration lot 99005 is being stored under room temperature and accelerated conditions. Data after three (3) months storage under accelerated conditions (40°C/75% RH) are presented in **Attachment C**. These data show that, after three (3) months, reported assay data remained within the release specification of 95-105% of the product label claim, and dissolution performance remained well above the specification of [redacted] thirty (30) minutes. Similarly, physical test results show no significant differences or trends.

Summary Data and Comparative Dissolution Profile. In **Table I**, the comparative analytical data from drug product produced by Danco (lot 99005), Roussel Uclaf (lots 29, 30 and 32), and the Population Council's clinical studies material (lot JMP 25524-109) are presented to assess their pharmaceutical equivalence. All five (5) lots of drug product were manufactured using the original RU drug substance synthesis and drug product manufacturing process. As shown in **Table I**, there are only minimal differences between the analytical data from the five (5) lots in each of the six (6) specification categories, supporting the conclusion of pharmaceutical equivalence.

Furthermore, the *in vitro* dissolution profiles of the Danco lot 99005 versus RU lot JMP 25524-109, previously submitted to FDA in Amendment 032, are equivalent. This data further strengthens the conclusion of equivalence between the Danco manufactured drug product and prior lots manufactured by RU. (**Attachment D**).

Graphs 1, 2, 3, and 4 show graphical presentations of the assay and dissolution data from the stability studies performed, including the on-going stability studies for Danco lot 99005. The data are presented from the zero time point, and extend to the longest testing interval encountered on the studies. These data show that assay data are consistently within the specification of 95-100% of product label claim, and show no downward trend over time. Similarly, the dissolution data are consistently above the release specification of not less than [redacted] released at thirty (30) minutes, and show no decline in dissolution rate over time.

All of the data reported for Danco lot 99005 show that tablet performance characteristics are consistent with the characteristics observed in the stability data generated by RU, including the continuing stability data generated on RU lot JMP 25524-109. Coincidentally, the RU licensed French manufacturer that is supplying the European market has received a thirty-six (36) month expiration period from the European Agency for a drug substance and drug product which, similar to Danco's contract manufacturers, also uses the RU drug substance synthesis and the RU drug product manufacturing process. Based on all the data presented in this amendment, as well as the anticipated data from the ongoing stability study, Danco believes that a thirty-six (36) month expiration period for the Danco drug product is reasonably supported.

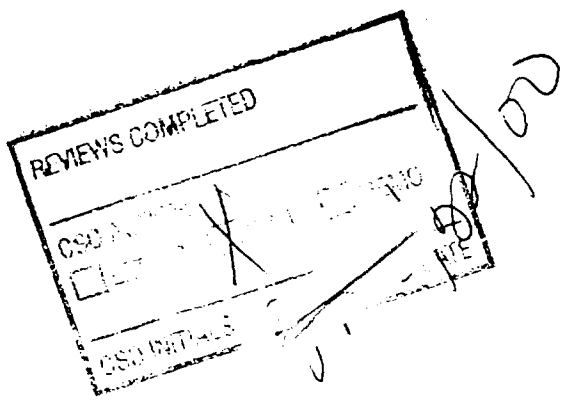
We request that the Division take all of these available data into consideration in making any determination of the expiration period for Danco's mifepristone tablets which we believe should reasonably be for thirty-six (36) months.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/dns
Enclosure

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council



The Danco Group

ORIGINAL

November 16, 1999

ORIG AMENDMENT

BC

NOV 7 1999

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

Reviewed
See Chem. Rev.
#3
1/31
2/19/00

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

- Amendment 036 - Supplemental Information to Drug Substance and Drug Product Chemistry, Manufacturing and Controls (CMC) Submissions

Dear

We are responding to your request for additional detail regarding the Drug Substance and Drug Product CMC submissions.

1. Certificate of Analysis of Roussel Mifepristone Lot 4V 1014 BJ.

   We are enclosing the Roussel Certificate of analysis for this lot (Attachment 1) . This is the lot that has been referred to in the Drug Substance CMC, submitted as Amendments # 025 and #028.

   Following your request, a reanalysis of a sample from this lot is currently underway. We will report those results as soon as they become available The method of analysis used is the same HPLC method that we have used previously both in China and at the U.S. testing laboratory and that is currently being re-validated in the U.S.

2. Certificates of Analysis for

   We are enclosing the certificates of analysis for the batches referred to in our Drug Substance CMC, submitted as Amendment #028 (Attachment 2).

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

3. Originals for the ———— in the Drug Substance CMC.

   Copies of this data were originally provided in our Drug Substance CMC, submitted as Amendment #025. The source laboratory of these data, ————, has reprinted their original data which are enclosed (Attachment 3).

4. Excipient Suppliers' Certificates of Analysis for Drug Product Batch # 99005.

   We are enclosing suppliers' Certificates of Analysis for those excipients that were utilized in the manufacture of Drug Product (Attachment 4). These data were included in the original Drug Product CMC, submitted as Amendment #032 and are provided here again for ease of reference.

5. Environment Assessment for Drug Product and Drug Substance.

   Since the expected introduction concentration (EIC) calculations for the Drug Product produced at — result in a value of — parts per billion (ppb) which is less than 1.0 ppb, the Tier 0 Criteria are met. (Attachment 5). We therefore request Categorical Exclusion from filing a formal Environment Assessment Section for the Drug Product manufactured at —

   We are awaiting the appropriate Environmental Compliance certificates for Drug Substance from Shanghai HuaLian Pharmaceutical Corporation. These are expected shortly and we will provide you with the information as soon as possible.

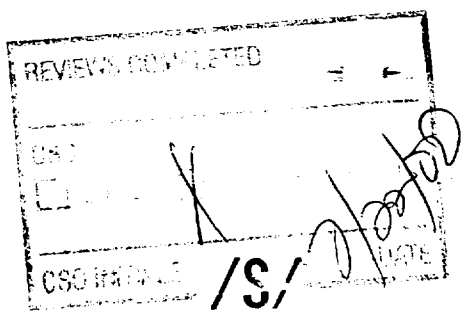
In addition, we are preparing the Methods Validation Packages for Drug Substance and Drug Product. This information will be provided together with samples of Drug Substance and Drug Product as well as a sample of the primary impurity in mifepristone, the ————

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

Sincerely,

/S/

President and
Chief Executive Officer



/dns
Enclosures

cc: ————
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

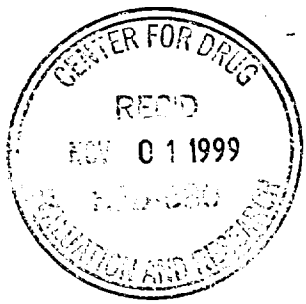
———— FDA

The Danco Group

October 28, 1999

ORIG AMENDMENT

BM



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

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

Dear

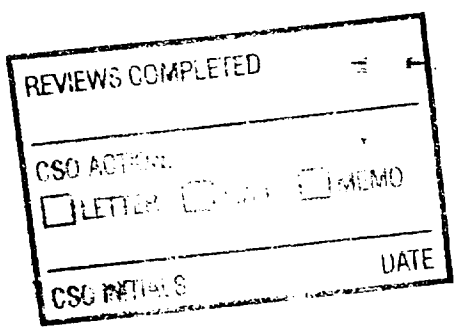
In response to your request for additional detail regarding planned distribution of mifepristone if it were subject to Subpart H, Sec. 314.520, we would like to refer you to Amendment 033, point #1 (enclosed).

In that Amendment, we provide a description of the proposed distribution process and in the 4th bullet refer to a letter that would need to be signed by physicians before they could be provided with mifepristone by the distributor.

We are now enclosing the above-mentioned letter for your review and comment.

Please let me know if you have any questions on the information provided.

Sincerely,



/dns
Enclosure
cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

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DUPLICATE

The Danco Group

October 28, 1999

ORIG AMENDMENT

BM

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

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

Dear

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Sincerely,

President and
Chief Executive Officer

/dns
Enclosure
cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

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ORIGINAL

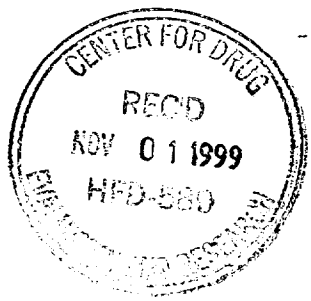
The Danco Group

October 28, 1999

ORIG AMENDMENT

noted 11/3/99 /S/

BM



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

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

Dear ———

In response to your request for additional detail regarding planned distribution of mifepristone if it were subject to Subpart H, Sec. 314.520, we would like to refer you to Amendment 033, point #1 (enclosed).

In that Amendment, we provide a description of the proposed distribution process and in the 4th bullet refer to a letter that would need to be signed by physicians before they could be provided with mifepristone by the distributor.

We are now enclosing the above-mentioned letter for your review and comment.

Please let me know if you have any questions on the information provided.

Sincerely.

———

———

President and
Chief Executive Officer

The details of the [proposed] distribution system for the product are in the process of being worked out with the proposed distributors.

/dns
Enclosure
cc: ——— – Danco Group
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

DAL /S/ 9/27/00

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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
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	October 28, 1999
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	CODE NAME *(If any)*
Mifepristone	Not available	

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

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: Drug Product Distribution

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 007597

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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1230 York Avenue
New York, NY 10021

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

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Mifepristone	Not available

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☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
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REASON FOR SUBMISSION
Drug Product Distribution

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

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The Danco Group

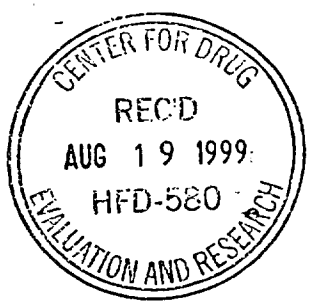
August 18, 1999

mailed
8/21/99
/S/

ORIGINAL

ORIG AMENDMENT

AZ



Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
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 033 - Remaining Responses to "FDA Approvable Letter of September 18, 1996." **Final Submission**

Dear

This Amendment 033 responds to the Approvable Letter points #1 on "Distribution", #8 on the final technical point on "Substance", #12 on "Phase 4 Commitments" and #19 on "Promotion". All the other points (15) from the Approvable Letter have been responded to previously.

For your easy reference, the attached Summary of Approvable Letter Points and Related Responses provides amendment # and date of submission for responses to each point from the Approvable Letter. We have additionally included separate sections for points 1 to 19 which list the FDA question or comment as well as the amendment number and date for the response to the FDA.

With the filing of Amendment 033, all the points raised in the Approvable Letter have been satisfactorily responded to and the NDA is now complete and ready for your final review.

If during the review process you have any questions on our responses, please don't hesitate to contact me.

Sincerely,

President and
Chief Executive Officer

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/dns
Enclosure

cc: [redacted]
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council
[redacted]
[redacted]
[redacted] FDA

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ DATE

APPEARS THIS WAY
ON ORIGINAL