

- Provide the distributor with as much information as possible if there is an ongoing pregnancy following completion of the treatment procedure and this pregnancy is not terminated.

In addition, the toll free telephone number will enable providers to request training materials and information, and speak to an experienced medical consultant about either a non-emergency patient issue or an urgent medical problem or possible complication. Through a separate routing on the toll free telephone number, patients will have access to general information about the product, a provider location near them and web page addresses for more information.

The final distribution system will be more fully developed in the next few months but will always attempt to insure that the drug is only supplied to qualified physician/hospitals who register with the distributor, that the patient is given access to the product label and that the product # is placed on the acknowledgment in the patient's file and that the anonymity of the patient is maintained.

Market launch will not occur until the distribution system is finalized and there are adequate systems in place to track shipment and use."

FDA requested six phase 4 studies of the applicant's August 22, 1996 (and reminded them of their commitment to perform them in the approvable letter dated September 18, 1996). The requested studies are listed below:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect of the regimen on children born after treatment failure.

The applicant's complete response was submitted to FDA August 18, 1999 regarding the requested phase 4 studies as follows:

"We are mindful of our Phase 4 commitments as outlined in the Population Council's letter to FDA dated September 16, 1996. We plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

2. Although the Council cannot commit to a study that follows all women who have surgical abortions following failed mifepristone abortion, we would propose to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time, for instance six months or one year. In such an investigation, we would classify women undergoing medical abortion according to whether they 1) completed their abortions successfully; 2) had a failed medical abortion and required a surgical abortion; 3) required surgical intervention for other reasons; or 4) were lost to follow-up.

We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifepristone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.
4. We are willing to supply treatment failure data from a sample of providers for a mutually agreeable period to time, for instance six months or one

year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under age 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those who smoke will be collected in the sample of women we have agreed to study, as described in item Number 2 and 4 above.
6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated."

Other issues raised by individual advisory committee members are addressed below:

While the DOSAGE AND ADMINISTRATION section of the labeling states that mifepristone may be administered by or under the supervision of a physician trained in abortion, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies, and with access to emergency medical facilities, the applicant has not mentioned anything about conducting training seminars for use of mifepristone, without financial incentive to physicians, and distributing the drug only to those physicians who completed the training. Perhaps the applicant will address this point when the details of the distribution system are submitted to FDA.

The applicant should be able to assess compliance with return visits of patients in the phase 4 studies to be performed.

A surgical termination, if needed, should be provided at no additional cost to the patient. It should be part of the mifepristone-misoprostol method of abortion.

Reasonable attempts to contact patients who do not return to confirm the abortion should be made by the physician.

The applicant intends to monitor the distribution system to ensure that only qualified physicians are treating patients.

The applicant will monitor the number of failed medical terminations and any resulting surgical complication.

The applicant will examine central registries of mifepristone users in Europe to determine what can be learned about multiple use. In addition, the applicant proposes to attempt to develop a cohort of women in future studies in the United States who report more than one use of the regimen and agree to be followed.

The applicant has some data on women who were more than 35 years of age, on women who smoked, and on women under 18 years of age. They will submit an analysis of safety and efficacy data on these subgroups. In addition, data on these subgroups will be collected during the phase 4 studies.

The outcomes of pregnancies not terminated by medical or surgical abortion should be followed up and reported by the physician. This should be part of the credentialing and distribution system.

Conditions of exclusions in the clinical trials are in the labeling.

There is no age restriction in the labeling. Women under 18 years of age or over 35 years of age were arbitrarily excluded from the clinical trials, but there is no biologic reason to think that the efficacy and safety of drug administration to these age groups is any different from that of women 18-35 years of age.

The labeling states that misoprostol should be taken two days after ingesting mifepristone.

Women who smoked at least 10 cigarettes per day were excluded from the French studies. Women in the French studies were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day misoprostol was to be administered.

Women in the U.S. studies were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Women were excluded from the U.S.

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studies if they were over 35 years of age, smoked more than 10 cigarettes per day, and had another risk factor for cardiovascular disease. The labeling contains a cautionary statement that women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone. The labeling does not contain a statement that alcohol and/or tobacco should be avoided during treatment. Myocardial infarction has been associated with the administration of an intramuscularly administered prostaglandin, sulprostone, but no such association has been reported with the administration of misoprostol. The labeling for misoprostol does not contain any statement regarding avoiding smoking.

Several comments regarding labeling were made by individual advisory committee members and have been thoroughly considered.

Overall, I do not think that the labeling imparts an impression to the physician or patient that the treatment regimen is "free of adverse effects and free of actually serious side effects."

The use of mifepristone and misoprostol extends the options available to women for the elective termination of early pregnancy, but it is inappropriate to directly compare this regimen with surgical termination in terms of adverse events. For example, bleeding and cramping are to be expected with mifepristone and misoprostol and not generally expected with surgical termination. The two methods are usually appropriate for abortion at different gestational ages. Medical abortions are done usually during the fifth to seventh weeks of gestation. Surgical terminations are usually not done before the sixth week of gestation.

Reference to drugs known to cause enzyme induction has been deleted.

The risk of malformation occurring if pregnancy is not terminated after drug administration appears in table 2 of the labeling.

The labeling states that a surgical termination must be recommended for patients who have an ongoing pregnancy because of the risk of fetal malformation resulting from the treatment procedure.

The physician labeling mentions that although specific drug interactions have not been studied, it is possible that interactions could occur with drugs like aspirin or other non-steroidal anti-inflammatory agents that modify or inhibit prostaglandin synthesis and metabolism. The only available study, however, found no evidence that non-steroidal anti-inflammatory drugs inhibit the ability of misoprostol to induce uterine

contractions and expulsions. In the patient labeling, the patient is instructed to advise her medical provider of all the medications she is taking and not to take any of them or any other medications during the treatment procedure without first telling her medical provider.

The mifepristone labeling states that since the effects of mifepristone on infants are unknown, and it is not known if misoprostol or its active metabolite is excreted in human milk, breast feeding women should consult with their medical provider to decide if they should discard their breastmilk for a few days following administration of the medications.

The labeling for misoprostol states that it is not known if the active metabolite (misoprostol acid) is excreted in human milk, and therefore, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Two days is the optimal time to administer misoprostol after the administration of mifepristone because mifepristone requires 36-48 hours to sensitize the uterine muscle to prostaglandins. This information could be added to the labeling.

We do not know if, or to what extent, effectiveness decreases if administration of misoprostol is delayed past two days after the administration of mifepristone. We do know that administration of misoprostol 36-48 hours after the administration of mifepristone is well founded, based on the mechanism of action. The labeling does state that misoprostol should be administered two days after administration of the mifepristone.

Most of the data available are from women 18 years of age or older. However, the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those over the age of 18 years.

Consideration should be given to including a statement under PRECAUTIONS in the physician labeling that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies of greater than 49 days.

Consideration should also be given to including a statement in the patient labeling under "Are there any reasons that I should not have the treatment procedure?" that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies greater than 49 days. This could follow the statements in the patient labeling that state,

"You should not have the treatment procedure if your medical provider determines that the duration of your pregnancy is more than 49 days. For many women this means that the first day of your last period was more than 49 days ago."

The physician labeling contains a PATIENT INFORMATION section that includes the statement, "Before giving you any medication, your medical provider will ask you to sign a statement that you have decided to terminate your pregnancy, and that you have read and understood this information." An ACKNOWLEDGEMENT is included in the PATIENT INFORMATION section for the patient and medical provider to sign. Consideration should be given to adding the statement, "My medical provider has confirmed that I am pregnant and that the pregnancy is not greater than 49 days" and a statement that, " My medical provider has discussed with me alternatives to medical abortion including surgical abortion and continuation of this pregnancy."

Everyone who was a member of the advisory committee when mifepristone was presented and who is still a special government employee was sent the results of the U.S. studies in the form of a copy of the article, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States" by members of the Population Council published in the April 30, 1998 issue of the New England Journal of Medicine. The article accurately and succinctly summarizes the results of the studies.

XIII. Recommendation:

Approval of this application is recommended provided that the labeling is satisfactorily revised and the complete details of the distribution system which are yet to be submitted are acceptable.

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[Redacted signature]
[Redacted signature] /S/ 1/27/00

APPEARS THIS WAY
ON ORIGINAL

SEP 13 2000

September 12, 2000

Mifepristone Tablets, 200mg
NDA 20-687

Population Council
Safety Update Report #3

Medical Officer's Review of Safety Update No. 3 Dated March 31, 2000

This NDA Safety Update Report summarizes the body of information which has been obtained by the Population Council since the cut-off date for the previous NDA Safety Update Report submitted August 3, 1999. The primary source of new information for this report is the Periodic Safety Update Report #9 prepared by [redacted] the [redacted] manufacturer of mifepristone, as well as from foreign clinical studies sponsored by the Population Council and from the literature. The cut-off date for this third report is February 29, 2000.

The report from [redacted] presents information from investigational and marketing experience with the product received by that company from worldwide sources. As stated in that report, there have been no specific actions taken with respect to the product for safety reasons such as rejection, withdrawal or suspension of marketing authorization, restrictions to distribution, suspension of clinical trials, modifications of dosage formulation, or changes in target population or indications. It is stated that in connection with new product approvals by European Union member countries via the mutual recognition procedure, some new textual changes were made to product labeling to reflect common usage practice and for purposes of accuracy and explanation.

One new area of safety concern is apparent in the new information presented in this NDA Safety Update Report. Following queries concerning the use of mifepristone in patients with acute hereditary hepatic porphyrias, [redacted] conducted an experiment at [redacted]. The chick embryo liver in ovo is a validated model system and currently used to identify "inducing" effects of drugs by measuring increases in hepatic delta amino levulinic synthetase, a rate controlling enzyme, resulting in overproduction of porphyrin and cytochrome P 450. Mifepristone crystalline powder was tested on that model and appeared to be highly toxic on the chick embryo liver. Therefore, [redacted] concluded that the drug should be contraindicated in patients with inherited porphyrias. This contraindication has been added to the updated Master Data Sheet dated December 1999 by [redacted]. It should be considered for inclusion in the labeling for Mifeprex as a contraindication, but since the contraindication would be based upon the results of a single nonclinical safety study, I am of the opinion that it does not warrant being in the labeling unless further confirmatory data becomes available.

The known number of subjects exposed to mifepristone in clinical studies for various indications is 32,439. Over [redacted] patients have received mifepristone in commercial distribution since its initial marketing in France in 1989. No clinical studies were conducted in the U.S. by the Population Council during the period covered by this NDA

Safety Update Report.

Protocol 171 (not conducted under an IND) has recently been completed in India for pregnancy termination in 900 women. There were no hospitalizations and no unexpected adverse events. Losses to follow-up were 3.5% and 4.4%.

Protocol [redacted] (not conducted under an IND) is ongoing [redacted]
[redacted]

Records have been maintained by [redacted] of ongoing pregnancies following administration of mifepristone and a prostoglandin for medical termination of the pregnancies. There are now reports of 107 ongoing pregnancies. Nine cases of fetal abnormalities have been reported as having occurred in association with these pregnancies. Eight of these occurred with the use of mifepristone and gemeprost. One occurred with the use of mifepristone alone.

Mifepristone is now approved for marketing in 21 countries.

The information contained in this Safety Update Report is consistent with the cumulative experience gained to date on mifepristone and does not reveal any unexpected, unanticipated safety issues that would change the benefit to risk ratio.

[redacted] /S/
[redacted]

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NDA 20-687
Population Council

Mifepristone 200 mg Oral Tablets
Review completed November 19, 1999

Medical Officer's Review of Safety Update Report No. 2 Dated August 3, 1999

This second NDA Safety Update Report includes accumulated information relative to the safety of mifepristone which has been obtained by the Population Council since Many 25, 1996, the cut-off date for the first Safety Update Report submitted on June 20, 1996. The cut-off for this second report is June 30, 1999.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the [redacted] manufacturers, Roussel Uclaf [redacted]. Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by [redacted] and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

[redacted]

Five periodic safety update reports are submitted covering the period December 1, 1995 - August 31, 1998. An estimated [redacted] patients received mifepristone under marketing conditions during this period.

In addition to the periodic safety update reports, international reports of adverse reactions have been submitted in two other formats: 1) two quarterly safety line listings of safety reports from clinical trials and [redacted] of the drug during the period of April 1, 1996 - September 30, 1996 when Roussel Uclaf was responsible for the drug and 2) five individual safety reports (and one follow-up report) received from Roussel Uclaf [redacted] that were reported to IND [redacted].

The periodic safety update reports provide a comprehensive summary of the safety information received by Roussel Uclaf [redacted] from worldwide sources during the covered time periods. Three of the five individual safety reports are also included in the periodic safety update reports. A total of 67 reports were received during a 32 month period when [redacted] patients received mifepristone. This is one report per [redacted] patients treated. A total of 28 of these adverse events were assessed as serious. This is one serious report per [redacted] patients treated. Five of these adverse events were some sort of urticaria or allergic reaction. One instance of disseminated intravascular coagulation was reported from the United Kingdom. Five

of the reports were of fetal abnormalities. The other reports were diverse. No unexpected safety issues are raised by this safety update report. Overall safety results are similar to those seen in the pivotal French studies and in the U.S. studies.

In the period since 1987, Roussel Uclaf [redacted] have received information on continuing pregnancies after administration of mifepristone or mifepristone and prostaglandins for medical termination of the pregnancies. A report, updated through June 1999, includes 87 reports of ongoing pregnancies, of which 26 followed the use of mifepristone alone and the remainder followed the use of mifepristone and a prostaglandin (or unknown). Nine reports of fetal anomalies have been received. Mifepristone alone was used in one report and mifepristone and gemeprost was used in eight reports. The one report of a fetal anomaly in a patient who received mifepristone alone resulted in a therapeutic termination of pregnancy with cleft palate and sirenomelia which was believed not to be drug related because of embryogenesis considerations. Of the nine reports of fetal anomalies, three occurred in babies at term. One had bilateral talipes (club foot), one had fingernail defect 3, and the third had a heart malformation. Fifteen of the 87 ongoing pregnancies were lost to followup.

A total of 33 normal babies have been born to women who received mifepristone alone (10), mifepristone plus misoprostol (11), or mifepristone plus some other prostaglandin (12). Data are too limited to determine whether mifepristone is a human teratogen.

Ninety articles published between 1996 and 1999 are submitted. These studies report the use of mifepristone in different clinical conditions, variable dosages, and for variable time durations. There is nothing reported in any of these articles that would change the safety profile of mifepristone for early abortion.

In the reports of early pregnancy termination, adverse events and efficacy reported are similar to that reported in the pivotal French studies and in the U.S. studies.

Unrelated to pregnancy termination, but of interest, are two reports where mild elevations in hepatic transaminases were noted in some subjects. Kettel reported 7 subjects with endometriosis treated with mifepristone, 5 mg daily for six months. Subjects with liver function abnormalities were excluded from treatment. One of the 7 subjects experienced a mild increase in liver transaminases. Perrault reported 28 subjects with untreated metastatic breast carcinoma treated with mifepristone, 200 mg daily. Mild elevations of AST were reported in 6 of the 28 subjects. (Six subjects had metastatic liver disease. It is not known how many, if any, of these subjects with metastatic liver disease were among the six reports of elevated AST.) These mild elevations in hepatic transaminases are of interest because some such changes were noted very early in abortion dose finding studies. However, 248 subjects in the U.S. studies had a full panel of laboratory tests at baseline and at visit 3 including alkaline phosphatase, AST, ALT, and LDH. The median changes noted were small and not of clinical significance.

The Clinical Expert Report on Mifepristone in Termination of Pregnancy is a review of the clinical documentation forming the basis for approval, key results from the published trials, and post-marketing surveillance data. It contains no new information.

We are informed that mifepristone was approved in eight countries (including Germany) July 6, 1999 under the mutual recognition procedure of the European Union.

No new areas of safety concern are apparent. Information contained in this safety update report is consistent with the cumulative experience gained to date from the pivotal French studies and the U.S. studies. The risk-benefit assessment remains unchanged.

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ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 28, 1996

Medical Officer's Summary of Safety Update Dated
June 20, 1996

Included in the Safety Update Report received June 27, 1996 are two new clinical study reports as well as new information regarding study reports previously submitted.

The first new clinical study report is entitled, "The Efficacy and Safety of Mifepristone 600 mg in a Single Dose in Combination with Intravenously Administered Sulprostone (Nalador) in Therapeutic Termination of Second Trimester Pregnancy". The second new clinical report is entitled "Role of Cortisol in the Thermal Response to Alimentation: Effect of Mifepristone" and consisted of twelve healthy, male volunteers, six of whom received a single 600 mg tablet and six of whom received a placebo.

Neither of the two new clinical study reports reveal any additional safety concerns not identified in the two pivotal clinical studies.

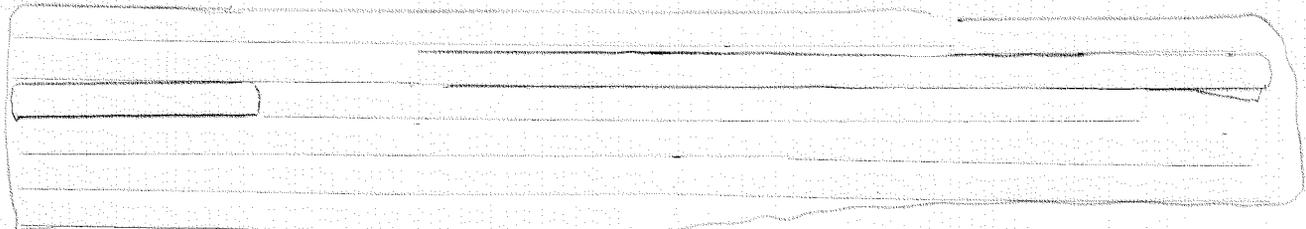
Newly completed clinical trials include three studies of labor induction, two studies of breast cancer, and the United States clinical trials of early pregnancy termination. Laboratory data from these completed studies have not yet been analyzed and, therefore, no information on laboratory data are reported in this safety update. Final data analysis and study reports for these six studies have not been completed. The results for termination of pregnancy studies conducted in the United States are expected to be in full agreement with the two pivotal clinical studies. No unanticipated safety issues were raised in these studies. Preliminary examination of information from the United States studies as it was forwarded weekly from the clinics directly to the sponsor during the course of the trials indicates that the final, analyzed results will be similar to those obtained in similar clinical trials of the same medical regimen.

The literature update includes eleven articles published in 1995 and one article published in 1996. Three articles are of particular interest. One is the publication of one of the pivotal clinical studies (FF/92/486/24) by Aubeny et.al. The second is entitled "A Comparative Analysis of Fall in Hemoglobin Following Abortions Conducted By Mifepristone (600 mg) and Vacuum Aspiration" by Thonneau et. Al. The investigators found significant blood loss in the two weeks following abortions by the mifepristone/sulprostone protocol while hemoglobin concentrations remained stable in women who had vacuum aspiration. Women who took mifepristone experienced a mean fall of 0.7 g/dl in hemoglobin two weeks after the abortion. The third article entitled "Clinical, Hormonal, and Sonographic Predictors of Successful RU-486-Induced Abortions" was by Menashe et.al. A small hematoma, seen as a localized detachment of the gestational sac, was observed in the decidua capsularis in women who aborted successfully. A significant decrease in plasma levels of estradiol and progesterone and significantly increased cortisol levels in the plasma of the patients who aborted were observed by the seventh day following treatment.

Table four of the Safety Update Report contains adverse reactions from all sources reported to Roussel Uclaf which were summarized in the quarterly line listings covering July 1, 1995 to September 30, 1995; October 1, 1995 to December 31, 1995; January 1, 1996 to March 31, 1996 and reported in the Periodic Safety Update No. 3 dated January 1996 for the period June 1, 1995 to November 30, 1995.

Of a total of forty eight patient reports of adverse experiences listed in Table 4, twenty-eight were reported from patients enrolled in the United States studies (protocols 166A and B). Of these twenty-eight reports, nineteen were metrorrhagia, three were abdominal pain, two were dehydration, and there were one each of depression, viral meningitis, vomiting, and syncope. Vacuum aspiration or D&C was performed in twelve cases of metrorrhagia and a blood transfusion was given in one case of metrorrhagia. Concomitant hypotension was also reported in four patients with severe metrorrhagia. The patient with syncope presented with a marked vasovagal reaction fifteen minutes after misoprostol administration.

In the section of the Safety Update Report entitled "Tolerance of RU 486 During United States Studies" there is Table 1 which was submitted to the sponsor by Russell Uclaf June 7, 1995 which indicates that there were forty-seven serious adverse events plus 8 non serious adverse events in the United States studies (protocols 166 A and B). Table 2 indicates that of the forty-seven serious adverse events forty-one were related to bleeding, two to hypotension, and one each to vomiting, chest pain, infection, and accidental injury.



Also included is a half page document entitled "Notifications Report to Roussel Uclaf from Study English PMS" which lists seven reactions occurring in five patients. There were three reports of uterine hemorrhage, one incomplete abortion with bleeding, one convulsion, one congenital nail disorder, and one report of lack of efficacy.

Also included is a section entitled "New Foreign Marketing Information" which consists only of a core product information document from the product manufacturer revised in March 1995.

Since the start of the use of mifepristone until November 30, 1995, Roussel Uclaf has recorded fifty-three cases of continued pregnancy after the intake of mifepristone for early pregnancy termination (alone or associated with a postaglandin analog).

Among these fifty-three cases:

Nineteen pregnancies were delivered at term (or close to it):

Fifteen were uneventful pregnancies with children normal at birth.

One was normal but born prematurely (33-34 weeks) from caesarean section

One was normal except for common slight bilateral talipes.

One case involves unilateral fingernail defects.

One child was reported as strictly normal at birth but it was known that when she was three months old, the infant was diagnosed as having an autoimmune disorder with chronic giant cell hepatitis and immunohemolytic anemia and later died of severe infectious pneumonia likely exacerbated by immuno-suppressive drugs.

The reporting physician's opinion (an expert in teratogenicity) was that the onset of the autoimmune disorder was coincidental and that the role of mifepristone could be reasonably excluded.

In fifteen cases information on further condition of the fetus was made available, mainly in the cases where pregnancy is known to have been terminated later:

In nine cases, termination was performed voluntarily and information either from histologic examination or from ultrasound was that the fetus was normal.

In one case, at therapeutic termination the fetus was noted to have sirenomelia associated with other fetal malformations. The opinion of the consulting embryologists to whom the case was submitted by Roussel Uclaf was that the role of mifepristone was very unlikely. This case has been published (Pons J.C. and all : Lancet, 1991, 328: 763).

In five cases of ongoing pregnancy, the latest available information during second trimester examination indicated normal pregnancy and fetus development.

In six cases, no information on the fetus could be obtained but pregnancy was known to have been terminated later.

In thirteen cases, no further information was made available; in most cases patients were lost to follow-up, and in some cases pregnancy is still ongoing.

Comment: This Safety Update does not reveal any unexpected, unanticipated safety issues that were not made known in the original submission of the NDA.

[Redacted] /S/

Concur: [Redacted] /S/ 9/11/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29, 1996

Medical Officer's Review of Safety Update Including a Summary Of International Post-Marketing Surveillance Data Dated July 25, 1996.

Submission dated July 25, 1996 contains summaries of all the safety information available to the sponsor from Roussel Uclaf International (France, Sweden, United Kingdom) post-marketing surveillance reports, starting from 1989, the first year mifepristone was on the market in France.

Spontaneous notification of suspected adverse events reported in post-marketing surveillance of mifepristone from June 1989 to June 1995 are listed in Table 7 of the submission. Causality by mifepristone is judged to be "unlikely", "unrelated", "not assessable", "insufficient data", "misuse", or "rumor" in the vast majority of cases. Adverse events that were possibly or probably related to drug use were usually expected events such as metrorrhagia. The most commonly used prostaglandin analogue during this period was sulprostone, given by injection.

The Mifepristone Safety Report covering the period January 1, 1991 through December 31, 1992 covers the first eighteen months since the launching of mifepristone in the United Kingdom. It also includes the period of discontinuation of sulprostone and the introduction in France of misoprostol as a possible alternative prostaglandin analogue. The report also contains the entire safety information available since [redacted] early pregnancy termination. In July, 1992, two new indications of mifepristone were approved in France, "therapeutic termination of second trimester pregnancy" and "labor induction in utero fetal death"; [redacted]

The International Safety Report Periodic Update from January 1, 1993 to May 31, 1995 contains no unexpected or unanticipated reports of adverse reactions that were not already known. There were no post-marketing phase IV or surveillance studies reported in final form during this period. There is mention of about three thousand four hundred and thirty-five patients enrolled in the post-marketing surveillance program conducted by Roussel Uclaf in the United Kingdom during the period of this report, but no additional information is available.

Periodic Safety Update Report No. 3 from June 1, 1995 to November 30, 1995 has been reviewed previously by the Food And Drug Administration Medical Officer and his comments are in his Safety Update Review dated August 28, 1996. No unexpected or unanticipated adverse reactions were found in this periodic report.

Comment: From the cumulative experience to date, no new special areas of concern have been identified. The assessment of the risk-benefit ratio of mifepristone is unaltered by the data included in this Safety Update Report.

[Redacted] /S/ [Redacted]

Concur: [Redacted] /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of United States Safety Data Dated July 14, 1996

Submission dated July 14, 1996 is a summary report of the serious adverse events from Protocols 166 A and B during the United States clinical trials. All of these reports have been submitted previously in IND

A total of fifty-two subjects had at least one SAE. There was more than one adverse event reported for most subjects. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least four subjects are listed in the summary below.

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth/ oxy.	IV Fluids	Transfusion	
52	13	Hemorrhage 41	34	15	28	04	26
		Faint/Dizziness 20					
		Cramping 14					
		Vomiting 06					
		Hypotension 05					
		Tachycardia 04					

These serious adverse events resulted in the hospitalization of twenty-six subjects. Four subjects received transfusions. A total of twenty-eight subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of thirty-four subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen subjects received methergine or oxytocin for treatment of bleeding, although eleven of these subjects eventually had a surgical procedure.

It is not possible to make a complete comparison of the serious adverse events reported in the United States trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the United States trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, at this time comparisons between the United States and NDA pivotal studies can only be made with the serious adverse events

reported from these fifty-two United States subjects, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire United States database. However, some general comparisons can be made. The total number of subjects enrolled in United States Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the United States trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metrorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by forty-one subjects in the United States studies. In the NDA pivotal studies, fifty-two subjects reported metrorrhagia or excessive bleeding, which was categorized as severe in twenty-one subjects. However, the manner in which the bleeding was treated differed in the two studies. In the United States trials, thirty-two of the thirty-four surgical interventions (D&C or aspiration) were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of fifteen subjects received surgical interventions for bleeding. The greater number of surgical interventions by United States investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the United States, but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The United States investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were five cases of hypotension, in the United States trials, although blood pressure readings were given for only two of these subjects. There were seven cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia for United States subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported in the United States subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the United States database.

Conclusion:

The SAEs reported during the United States trial do not appear to differ significantly from those reported in the pivotal NDA trials, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the United States trials may be explained by the initial inexperience of United States clinicians in providing medical abortion. Investigators in the United States trials have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies.

In summary, the current comparison of SAEs between the United States trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of United States settings.

[Redacted] /S/ [Redacted]

Concur: [Redacted] /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL