Reproductive Health Drugs Advisory Committee

FDA Technical Center
Gaithersburg MD
19 July 1996

AGENDA

0900-0905 Opening comments. Confirmation of subsequent meeting dates: 20-22 November 1996; 13-14 February 1997; 5-6 June 1997.

NEW DRUG APPLICATION (NDA) FOR THE USE OF MIFEPRISTONE FOR INTERRUPTION OF EARLY PREGNANCY

0905-0915 Opening comments
David A. Kessler, MD
Commissioner of Food and Drugs

0915-1200 Presentations by the Sponsor, The Population Council (PC)

Sandra P. Arnold, BA (Mathematics)
Vice-President, Corporate Affairs (PC)

Ann Robbins, PhD
Scientist, Center for Biomedical Research (PC)

Irvin M. Spitz, MD
Senior Scientist, Center for Biomedical Research (PC)

C. Wayne Bardin, MD
Independent Consultant

Beverly Winikoff, MD, MPH
Program Director
Reproductive Health Programs Division (PC)

Elizabeth Newhall, MD
Medical Director, Downtown Women's Center
Portland, Oregon

1200-1300 Presentations by the FDA Reviewing Division

Introduction
Lisa Rarick, MD
Acting Director, Division of
Reproductive and Urologic Drug Products

Review of pharmacology and toxicology findings
Alexander Jordan, PhD
Pharmacology Team Leader

Review of non-US clinical findings
Ridgely C. Bennett, MD, MPH
Medical Officer

Review of US clinical findings and considerations for use
Lisa Rarick, MD

1300-1400 Lunch

1400-1630 Open Public Hearing

Private citizens or representatives of the following organizations (except for Congressman Coburn's office) contacted the Agency before 5 pm EDT on 12 July to request time to speak:

1. Office of Congressman Tom Coburn
   Member, U.S. House of Representatives, Michael Schwartz
2. Alan Guttmacher Institute
   Lisa Kaeser, JD
3. American College of Obstetricians and Gynecologists
   Carolyn L. Westoff, MD
4. American Life League, Inc.
   Rebecca Lindstedt
5. American Medical Student Association
   Paul Jung, MD
6. American Medical Women's Association
   Diana Dell, MD
7. American Public Health Association
   Allan Rosenfield, MD
8. American Victims of Abortion
   Olivia L. Gans
9. Baruch College
   Joel Brind, PhD
10. Private citizen
    Randy O'Bannon, speaking for Charles Cargille, MD
11. Center for Reproductive Law and Policy
    Janet Benshoof, JD
12. Helen M. Donovan, JD
    Private citizen
13. Family Research Council
    Gracie S. Hsu, MHS
14. Feminist Majority Foundation
    Eleanor Smeal
15. Feminist Women's Health Center
    Marie Head
16. Jones Institute for Reproductive Medicine
    Gary D. Hodgen, PhD
17. Life Issues Institute
    Richard D. Glasow, PhD
18. National Abortion and Reproductive Rights League
    Marcy J. Wilder, JD
19. National Abortion Federation
    Paul Blumenthal, MD

20. National Association of Nurse Practitioners in Reproductive Health
    Susan Wysocki, RNC, NP
21. National Council of Jewish Women
    Donna Gary
22. National Organization for Women, Inc.
    Janice E. Erickson
23. National Women's Health Network
    Cynthia A. Pearson
24. National Women's Health Organization
    Susan Hill
25. National Women's Law Center
    Ann Koller
26. Northeast Waterloo Family Practice
    M. Louviere, MD
27. Pharmacists for Life, International
    Mary Jasinski Caldwell
28. Planned Parenthood Federation of America
    Gloria M. Feldt
29. Planned Parenthood of Westchester and Rockland, Inc.
    Lynn Borgatta, MD, MPH
30. Reproductive Health Technologies Project
    Marie Bass
31. Private citizen
    Wendy Simonds, PhD
32. Society of Physicians for Reproductive Choice and Health
    Seymour L. Romney, MD
33. Southwestern Medical Clinic, PC
    Donna J. Harrison, MD
34. Women's Legal Defense Fund
    Joanne L. Hustead

1630-1645 Break

1645-1845 Discussion and response to questions

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS
CENTER FOR DRUG EVALUATION AND RESEARCH

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Former committee members with terms ending 6/30/96 attending this meeting as Consultants:

Daling, Janet R., Ph.D. 6/30/96
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1124 Columbia Street (MET 381)
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Albert Einstein College of Medicine
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Consumer Representative:
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Adjunct Assistant Professor
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University of California, N631Y
San Francisco, California

FDA Guest Speaker:
Ricardo Azziz, M.D., M.P.H.
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
University of Alabama at Birmingham
Old Hillman Building 549
618 South 20th Street
Birmingham, Alabama 35233-7333

July 19, 1996

Reproductive Health Drugs Advisory Committee

FDA Technical Center
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QUESTIONS

The regimen proposed for the use of mifepristone for the termination of early pregnancy consists of the oral administration of 600 milligrams of mifepristone within 49 days after the beginning of the last menstrual period, followed by oral administration of 400 micrograms of misoprostol 48 hours later.

1. a. Do the results of the open-label, historically controlled studies conducted in France establish the efficacy of this regimen for use in the United States?
   b. If not, what additional efficacy information should the applicant provide?
2. The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience.
   a. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication?
   In your discussion, please include comments on the following issues:
   - *Whether the adverse events associated with the regimen can be adequately managed when the regimen is administered as labeled.*
   - *The acceptability of the frequency of adverse events.*

   b. If not, what additional safety information should the applicant provide?
3. Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States?
4. If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who receive it to be appropriate?
5. If the regimen were to be approved, what further information, if any, do you recommend be included in the written information to be provided to the patient?
6. If the regimen were to be approved, do you have recommendations concerning the drug distribution system proposed by the applicant?
7. If the regimen were to be approved, what recommendations, if any, do you have for post-marketing studies?

DOCUMENTS CONNECTED WITH THIS MEETING MUST BE REQUESTED
IN WRITING FROM THE
FREEDOM OF INFORMATION OFFICE

Mail written request specifying date of meeting, name of committee, and a description of the documents requested to:

Food and Drug Administration
Freedom of Information Staff
HFI-35, Room 12A-16
5600 Fisher's Lane
Rockville, MD 20857

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HFD

Adv. Committee for Reproductive Health Drugs
July 19th

To The Advisory Committee For The F.D.A.:
C/O Mr. John Tracy.

I believe that the psychological impact and other ramifications of RU486 is more important than that of the physical. The medicine may be seen as a sychological hypnogent, and it could put great dangers upon our Country.

July 20, 1996

Some people may get a pleasure out of their suffering such as in jail, hurting people, destroying things to cause a reaction in others etc. because it gives them a satisfaction from which they feel an emptiness in what they consider to be their main natural pleasure, and that is based upon sex. However, they will say the following about sex: "A man will reach his peak at the age of 17 years old, and after that it's all down hill." Unbeknownst to them, however, when a man obeys God's Laws about sexual things, his peak is never reached, and they say the following: "It gets better and better, bigger and bigger every time."

This void which the violators of God's Laws in sex work toward is a self-punishment in their mind and soul as described below. They wish to fill this void with a something which gives them the satisfaction which they miss in their sexual acts. This something is an evil because the actual definition of evil is the absence of something or anything which is not of the truth, the right, and the good; i.e., an evil is the absence never the presence of anything, and is classed in such a way as to mean that it is non-existent essentially. The more such people participate in this deviation from nature (i.e., the evil use of sex) the worse the void gets, and the more they feel the absence in their mind and soul (i.e., their being). They turn, then, to other evils for satisfaction only to experience more evil (or the absence of the good) in their minds and souls. Sometimes the evil is so great, such as committing murder, that it produces a new level of evil in their being (i.e., in the soul and mind) which for a time produces a new level of a void which in turn produces a new kind of satisfaction. But a sparing and sparse use of it comes about by way of a fear that the new satisfaction will decrease as that which happens with all evils. This quest in the being (mind and soul) of an evil bent person results in what the secular law refers to as criminal insanity, and in general, domestic violence starts here too.

In conclusion, we may now show how and why such people will choose to go to Hell rather than to be with God in Heaven. Those

people want evil because of the pleasure it gives, and of course the road which they feel that they must travel is that of evil because of the following facts (Note: To define a negative or that which is not it is accomplished better by defining that which is, or the positive which is involved, then point to its contrary): To obtain a real satifaction in a person's being (i.e. the mind and soul), he must know that only a good can come from a good because the good will always produce more good -where an evil is an absence- for to the contrary, nothing can ever come from nothing as far as a human being is concerned. This means that in order to be good, a thing must have existence no matter the quantity. The pleasure of/in the good is the quest always to improve upon that good which brings about a satisfaction because the existence of the good has increased. Also, just as in eating a hearty meal (a good meal), merely the smell (order) of it alone will increase a person's appetite, and the more a person eats of what they had smelled, the more the satisfaction tends toward being complete. There is no difference in any other good of any kind if indeed it is truly a good.

Any kind of evil in sex may be referred to as an adultery because it produces a lessness of it (i.e., an evil) so that even the practice of birth control in any of its forms is an evil, and it will produce chaos in a person's mind and soul (i.e., his being). In May of 1930, God told a small child that, "Most people are going to hell because of sins of sex." Then He told the child to put this in his own words so that the evil bent people would not be able to change it. The child (now grown) says: "Almost everybody (all people) are going to hell because of sins of sex." This means that because God loves everyone, and He would not hurt anyone by sending them to hell by Himself, those people —"most people"— will send themselves to Hell if not immediately, then eventually, and for all eternity. This tendency for people to hurt themselves will not change after death because we are whomsoever we are including absulutely everything which we are right now.

When a person who is in a quest for satisfaction by way of evil, the main desire which they have when they are faced with the good, is to destroy the good, and therefore they feel that they may possess it, because

that is the only reward in time and space which they know in relation to a satisfaction of any kind. This is especially significant in relation to the soul of a person in that when an evil bent person comes in contact (i.e., he experiences the presence of) with a good person (in his soul), the main feeling in the evil bent person is to have a possession by destruction, in other words, he wishes to create a void for the purpose of satisfaction.

The only help which such people have upon this Earth is an appeal to Almighty God Himself because He said: "Ask and you shall receive, seek and you shall find, knock and it shall be opened to you." (Note: Saint Francis Of Assizi made it all the way back, and is well worth copying.)

Sincerely Yours,

Francis

F.R.Gamache PhD
P.O. Box 40538
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Acceptability of Mifepristone Plus Misoprostol for Medical Abortion

The Population Council
Preliminary/unpublished data
Presented July 19, 1996
to FDA advisory committee

Best Features (Previous Studies)

- No surgery
- No anaesthesia
- No pain / comfortable
- Natural
- Less risk
- Easy / convenient
- Private
- Very early

The Population Council
Preliminary/unpublished data
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Do Different Kinds Of Women Have Different Reactions?

- There were no differences by race, ethnicity or method of payment for medical care
- Analysis not yet done by geography

The Population Council
Preliminary/unpublished data
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Acceptability of Mifepristone / Misoprostol to Providers

- Focus group of providers in each clinic
- 78 Providers: MDs, RNs, other clinicians, counselors, administrators
- 17 Clinics
- 15 States

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Preliminary/unpublished data
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Acceptability of Mifepristone / Misoprostol to Patients

- Almost 800 women seeking abortion
- ≤ 49 days LMP
- Study volunteers
- 17 clinics / 15 states
- About one third minority

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Preliminary/unpublished data
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Careful Introduction

- Extensive provider education in medical abortion
- Distributed directly to providers
- Physicians who have had training in:
  - — dating of pregnancy
  - — diagnosis of ectopic pregnancy
  - — surgical abortion
- Physicians with access to facilities for surgical abortion and emergency treatment

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Drug Administration

- Stocks of drug in secure location
- Record kept of each dose administered
- Patient information in each package
- Administration of medication on site and under supervision

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General Reactions to Medical Abortion Experience

- Majority of women (~60%) prefer medical regimen in most studies
- Very high levels of satisfaction
- Very high willingness to use again and recommend to others

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How Does This Compare to Previous Abortion Experience?

- More than 9 of 10 reported this as more satisfactory
- About two thirds of women for whom it failed reported it as more satisfactory

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Preliminary/unpublished data
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How Satisfactory Was This Abortion Procedure?

- More than nine out of ten women were very satisfied or satisfied
- Less than 3 in a hundred were unsatisfied, half of these women experienced treatment failure
- Even among those for whom it did not work, two thirds were very satisfied or satisfied

The Population Council
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Mifepristone / Misoprostol for Early Abortion: A New Type of Therapy

- Women like this method (overwhelmingly)
- Very different experience / technology from available alternatives
- U.S. women react similarly to women in other places
- Providers want to offer it

The Population Council
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- **Mifepristone / misoprostol is a safe, effective, and highly acceptable therapy for women seeking early abortion.**
- **U.S. physicians want to offer it, thereby increasing access to services.**
- **Women will have more choice, and abortions will be earlier and therefore safer.**

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Measures Of Acceptability

- Was it what you expected?
- How does it compare to previous experience?
- Would you use it again?
- Would you recommend it to others?

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Acceptability Studies of Early Medical Abortion Outside U.S. 1979 – 1993

- 12 reports
- 6 countries
- Generally small cohorts (< 100)
- Experimental regimens
- Findings consistently and strongly support very high preference by women

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A New Method:
Issues For Providers

- May be time consuming: extra time for counseling
- Not used to waiting for results of treatment
- Not used to observing patient bleeding
- May be complicated to serve medical and surgical abortion patients simultaneously
- Need for extra space and bathrooms

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Perceptions Of Bleeding

- Most common answer was that both length and amount were "as expected"
- Next most common answers were longer and more than expected
- Women for whom method failed tended to report more and longer bleeding

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Perceptions Of Pain

- More than half of women reported the experience as less painful than expected
- The next most common response was that the experience was "as expected"

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Provider Attitudes to the New Method

- Providers want to offer this method
- Providers think women like this method
- Providers feel they get better at giving the method with practice
- Providers become even more positive about the method with experience

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Providers Become Even More Positive about Method with Experience

- "I really didn't expect to like this... I thought it would be very time consuming and I was really amazed at how easy it was and how much women liked it." (MD)

- "Most of us said that we'd never do it... And then I realized, no, I'd take mifepristone... I'd rather do this instead of taking my chances with who knows who out there [surgically]." (MD)

- "... that was the learning experience for me — was that this was a plus for so many women..." (Counselor)

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Providers Feel They Get Better at Giving the Method with Practice

- "... the learning curve just in dealing with this from the clinic's point of view, from the doctor's point of view... I learned a lot..." (MD)
- "... I definitely noticed a big shift as we all got familiar with it as a clinic. Overall, I think patients did better because of what we could provide with our knowledge." (Study Coordinator)
- "... we weren't very efficient at the beginning... at the end it was beautiful because we'd hardly done as well at the beginning as we did at the end." (Health Worker)

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Providers Think Women Like This Method

- Most providers thought women preferred it overall
- "Even the ones that failed and even the ones I thought had a terrible experience in terms of the physical symptoms, for the most part said, 'I would do it again... I like this method'." (Nurse Practitioner)

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Providers Want to Offer This Method

- "I desperately want it here...I would offer the option." (Senior Clinician)
- "The best thing was to be able to answer the phone and be able to tell people who were really scared about having a surgical procedure that there was another alternative." (Administrative Coordinator)
- "I had spent the previous twenty-two years working for an abortion clinic doing surgical abortion... and had listened to women ask, 'Isn't there some other way?'" (Office Manager)

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Patient Reactions: Control / Autonomy

- "It offers a lot more control."
- "*You* take the medication."
- "Your body does it itself."
- "I was the primary person knowing when I was actually aborting."
- "This was more *my body* discharging it than someone going in."

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Potential to Increase Access to Services

1995

- 33% of all U.S. OB / GYNs provide abortion services
- 66% increase in OB / GYN providers if mifepristone / misoprostol were available in U.S.

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Patient Reactions:
Avoidance Of Surgery / Anaesthesia

- "I didn't like the idea of a surgical abortion."
- "I don't like any type of surgery at all."
- "I've had anaesthesia. I didn't like it."
- "Anything that didn't involve anaesthesia."
- "I want to try it anyway, even if I have to go through the other at the end..."

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Patient Reactions:
"Natural"

- "I've had a miscarriage before. It's just like having a miscarriage."
- "It doesn't make you nervous."
- "More humane."
- "It felt like my period, so it felt like a natural process."

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Reasons Patients Value Medical Abortion

- Avoids surgery
- More "natural"
- Preserves control / autonomy

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Unwanted pregnancy is a serious and stressful problem for women

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Was Your Experience Similar to What You Thought Would Happen?

- Half thought it was just what they expected
- One third thought it better
- One in eight thought it worse

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Was There Any Problem with the Timing or Place of the Abortion?

- Less than one in twenty-five said there was a problem

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Would You Choose the Same Procedure Again?

- More than 9 in 10 said "yes"
- More than three quarters of women for whom it failed said "yes"

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Would You Recommend This Method To A Friend Or Relative?

- Almost everyone said "yes"
- More than four out of five of women for whom it failed said "yes"

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Safety of

Mifepristone Plus Misoprostol

for Medical Abortions

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Medical Termination of Pregnancy Requires:

- Withdrawal of the progesterone support of the endometrium
- Increased contraction of the myometrium

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Contraction of the Myometrium

- Contraction is regulated by the balance between the inhibitory action of progesterone and the stimulatory action of prostaglandins
- During pregnancy progesterone suppresses contractions
- Mifepristone increases the action of prostaglandins

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Rationale for Reporting Adverse Events for the Mifepristone / Misoprostol Combination

- There is evidence for synergy between mifepristone and misoprostol
- Symptoms of pregnancy are increased by both drugs
- No multicenter studies of oral misoprostol alone during pregnancy

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Overview of Safety / Adverse Events

- Animal studies showed no toxic effects
- In humans, there were no deaths or serious cardiovascular outcomes
- In humans, no unexpected adverse events occurred
- Virtually all adverse events were related to the pharmacological actions of the regimen and some of these actions are essential for efficacy

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Severe Adverse Events

Severe as judged by women	Severe medical outcome
• bleeding	• cardiovascular event
• uterine contractions	• hospitalization
• nausea / vomiting	• surgery
• diarrhea	• blood transfusion

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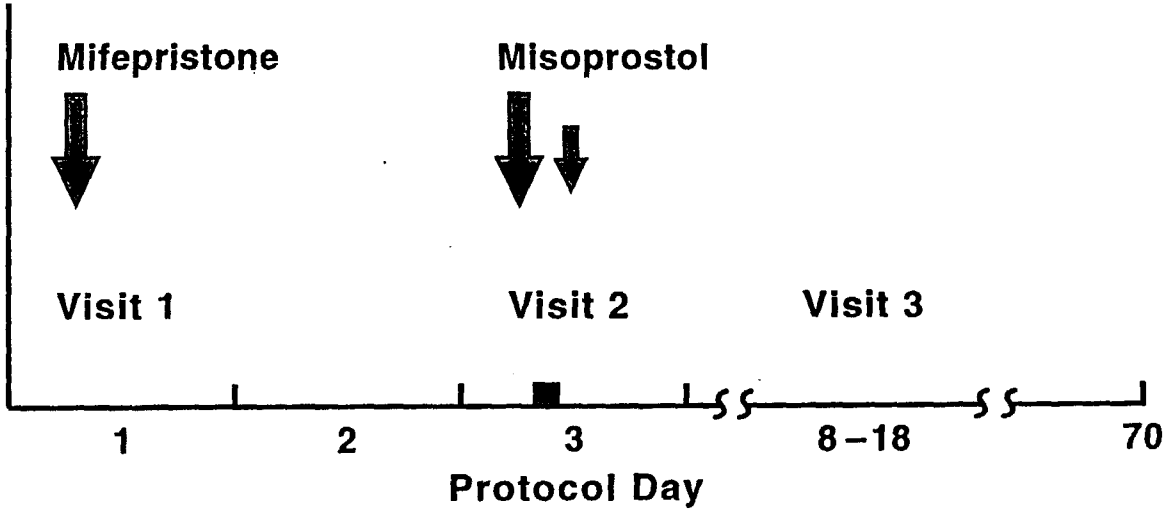

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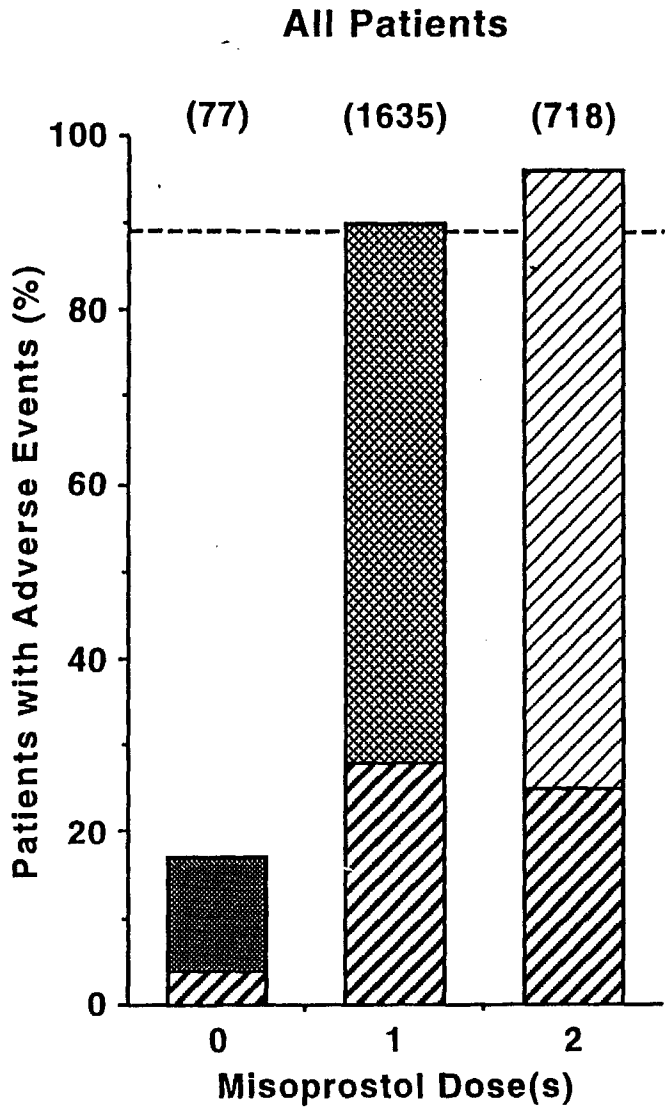

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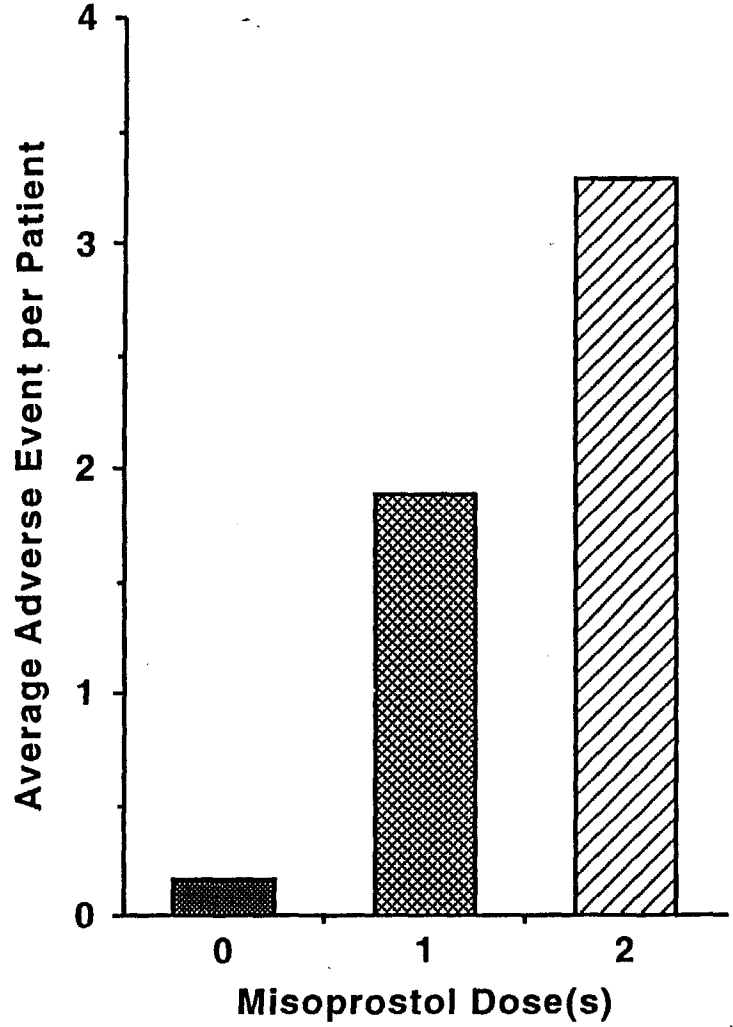

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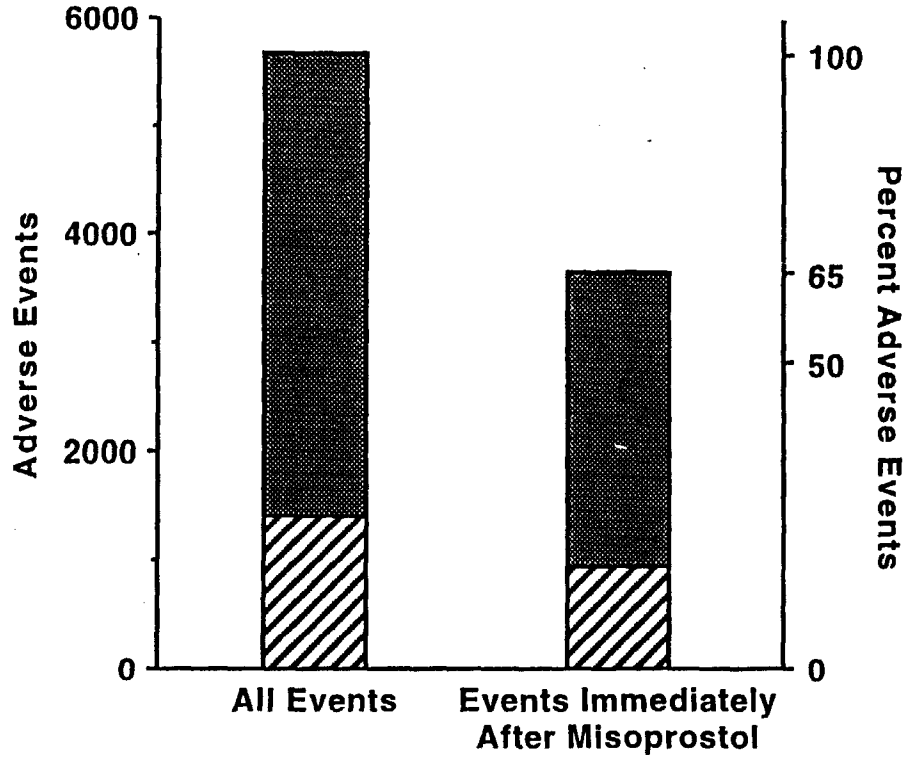

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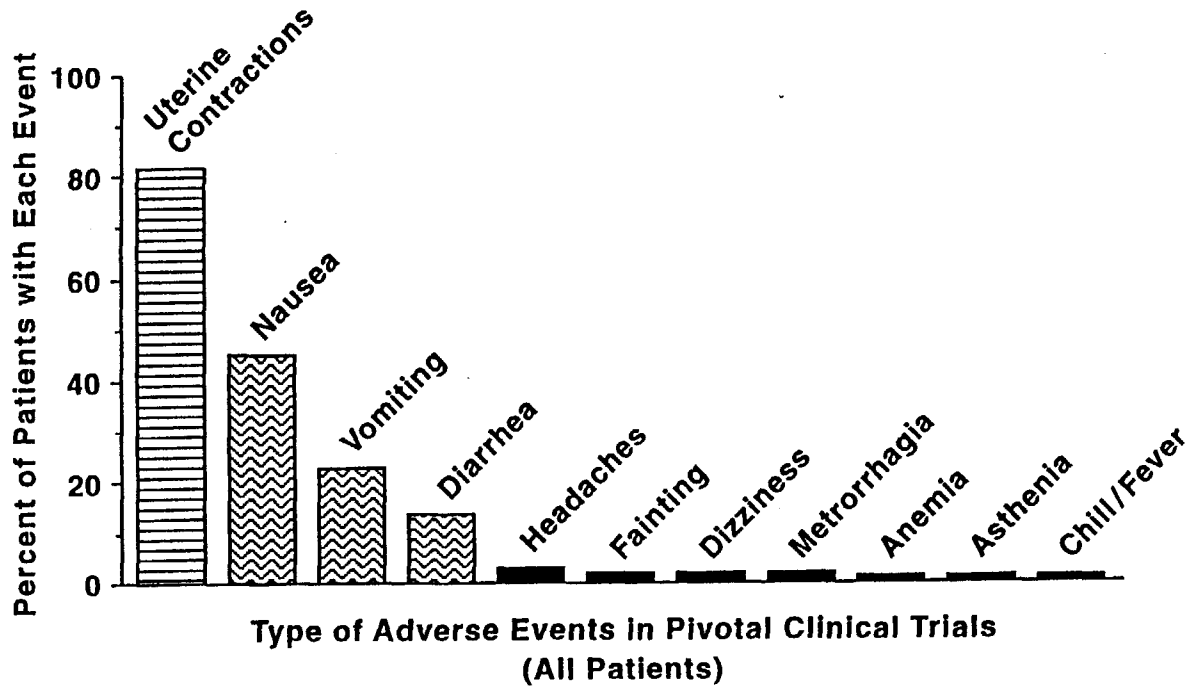

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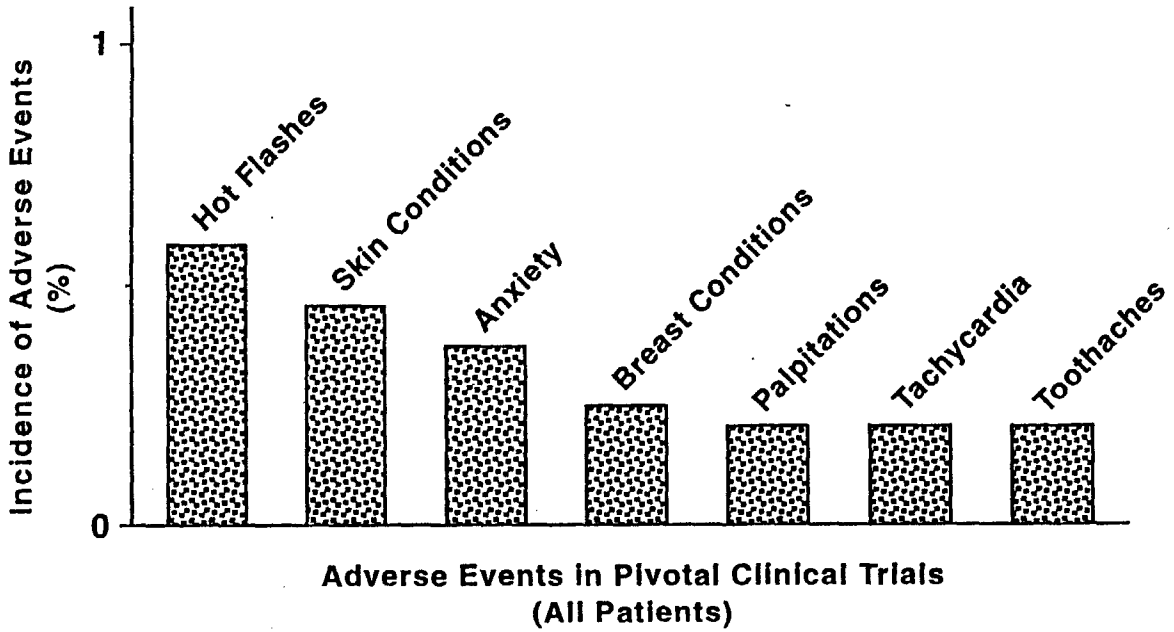

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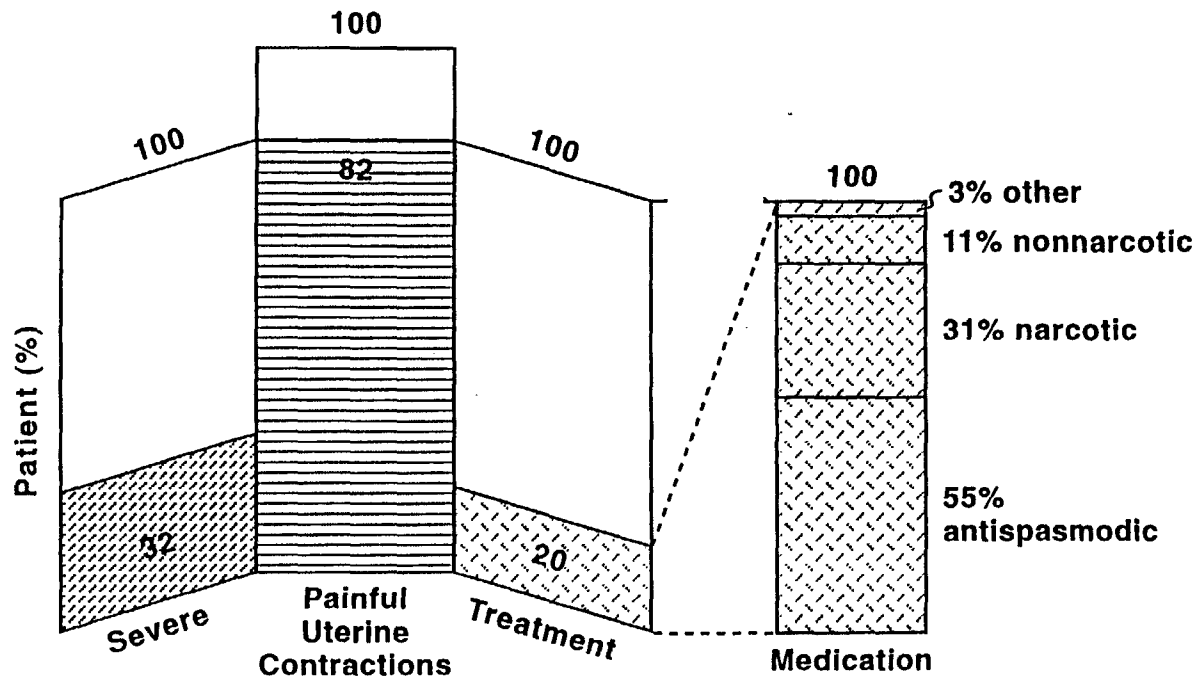

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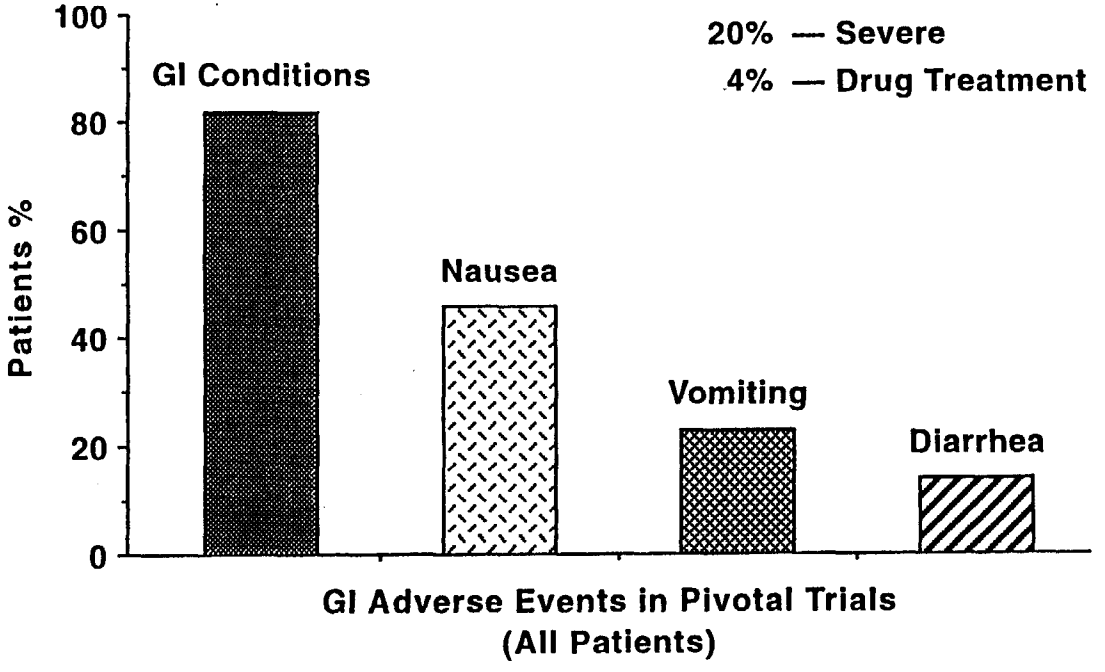

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Bleeding Expected as Part of Treatment Procedure

- 96.6% of all patients bleed
- 33% bleed prior to misoprostol
- Mean duration — 9.1 ± 0.09 days
- Longest duration — 69 days

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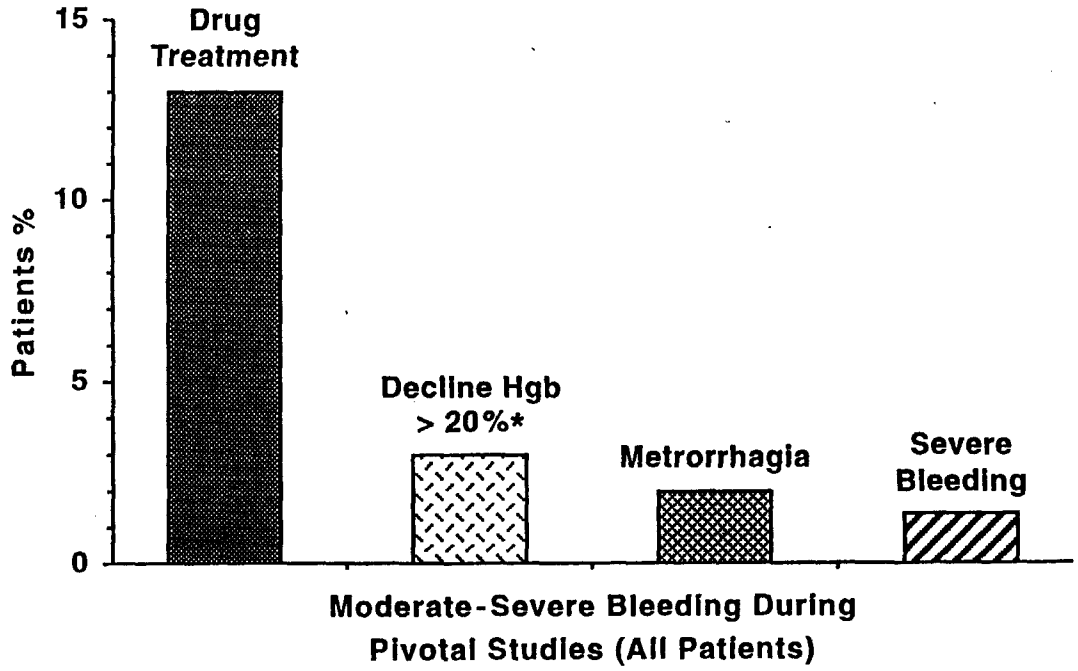

* at 8–18 days

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Treatment for Severe Bleeding Events

Treatment	No. Patients
Hospitalization	21
Surgery	15
Transfusion	4

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Cardiovascular Events

Event	Number	(Severe)
• Decline in BP > 20%	420 *	
Hypotension	7	(1)
• Increase in BP > 20%	396 **	
Hypertension	8	
• Tachycardia	5	(1)

*17% **16%

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Comparison of Serious Adverse Events (SAE)* in the U.S. Clinical Trial and NDA Pivotal Trials

	U.S.	French
No. subjects enrolled	2121	2480
No. of hospitalizations	26 (1%)	21 (1%)
No. of transfusions	4 (<1%)	4 (<1%)
No. of subjects with hemorrhage	41 (2%)	52 (2%)
Surgical intervention for bleeding	32 (2%)	15 (1%)

*reported on Medwatch form to the FDA

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Conclusions

- The risk of adverse events has been determined in two pivotal studies. As a result, labeling has been written that informs women about the risks of this regimen.
- The most frequent adverse events, painful uterine contractions and GI symptoms, were expected outcomes of the regimen.
- 65% of events were immediately after misoprostol at the 2nd visit.

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Conclusions

- 80% of women required no pain medication.
- Bleeding occurred in all women with a successful outcome. Rarely, excessive bleeding requiring hospitalization, transfusion or curettage occurred.
- Cardiovascular events including clinical hypertension, hypotension, and tachycardia were rare and only 2 were considered severe — these resolved without long term consequences.

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Effectiveness of Mifepristone Plus Misoprostol for Medical Abortion

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Study Regimens

- Mifepristone alone
- Mifepristone and Prostaglandins
  - — Sulprostone or Gemeprost
- Mifepristone and Misoprostol

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The first published study showed pregnancy termination in 9 of 11 women with duration of gestation of less than 56 days following mifepristone administered in a dose of 200 mg daily for 4 days.

(Herrmann et al, 1982)

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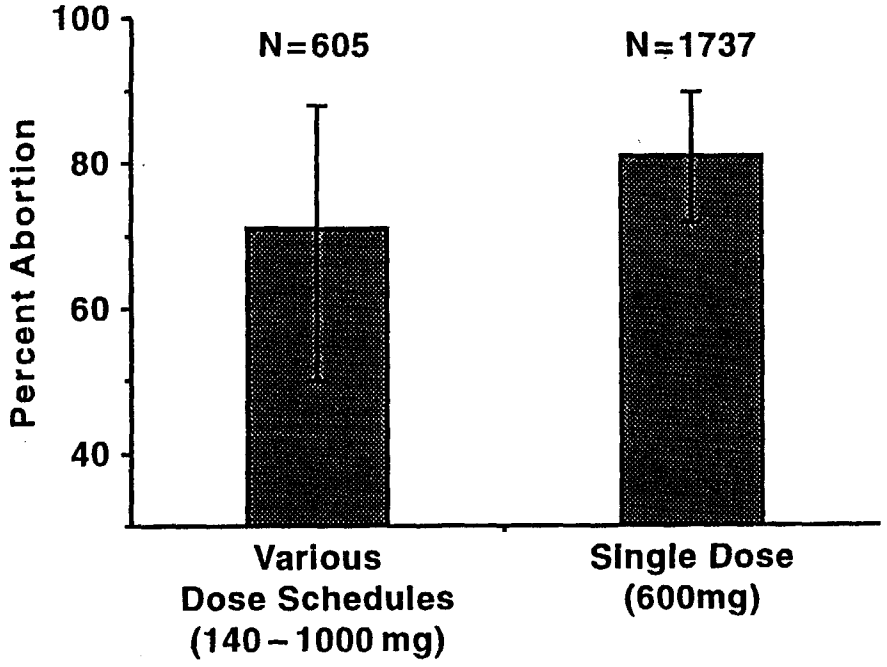
Complete Medical Abortion after Mifepristone Alone
Duration of Gestation ≤ 49 Days



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Uterine activity is controlled by a balance between the intrinsic inhibition of progesterone and stimulation by prostaglandins.

(Csapo, 1973)

Mifepristone increases the sensitivity of the myometrium to prostaglandins.

(Bygdeman and Swahn, 1985)

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Prostaglandins Used

	Sulprostone	Gemeprost	Misoprostol
Type of analog	PGE_2	PGE_1	PGE_1
Mode of administration	parenteral	vaginal suppository	oral
Refrigeration	yes	yes	no
Cost	$$$$	$$$$	$
Available in US	no	no	yes

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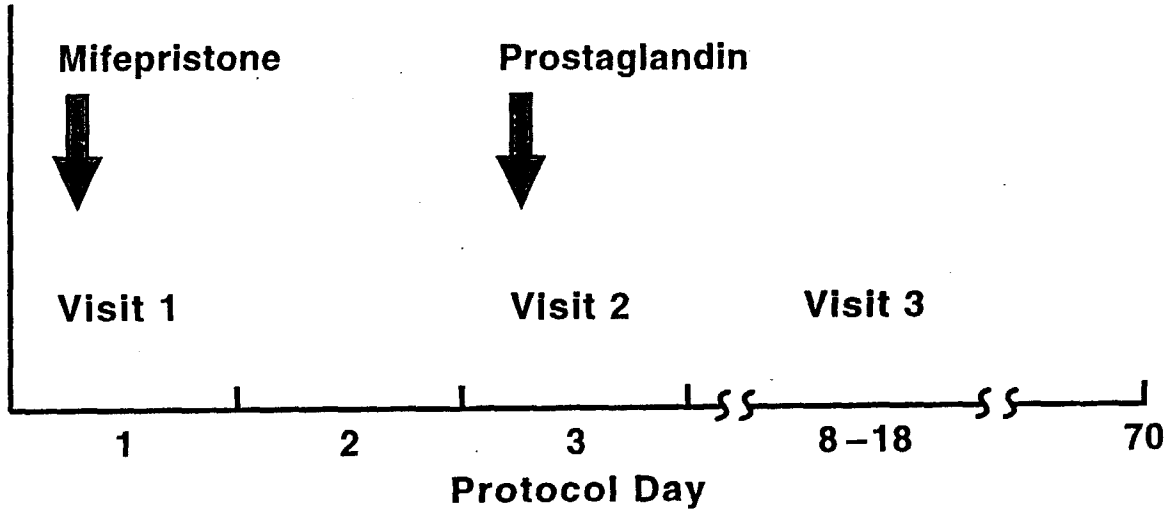

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Pregnancy Termination with Mifepristone and Prostaglandins: Literature Review

Duration of Gestation ≤ 49 Days

Prostaglandin	No. enrolled	Successful medical abortion (%)
Sulprostone	> 15,000	95.7
Gemeprost	> 2,000	95.5
Mifepristone alone	> 1,700	81.0

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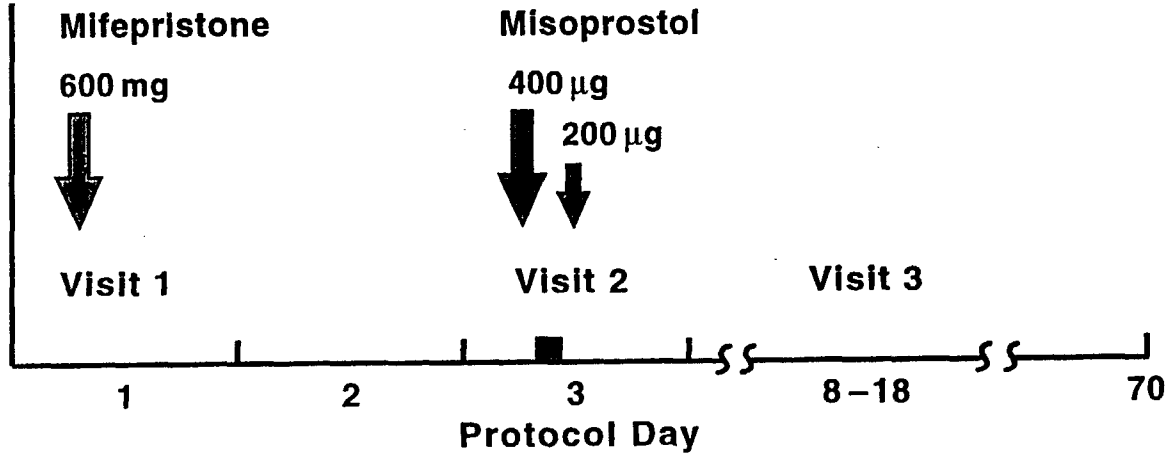
Pivotal Studies

- Study I: gestation (days) ≤ 49
- Study II: gestation (days) ≤ 49, 50 – 63] extra dose

] efficacy] safety



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Pivotal Studies

	Study I	Study II
Duration of gestation	≤ 49 days	≤ 63 days
Day 1: mifepristone	600 mg	600 mg
Day 3: misoprostol	400 μg	400 μg; if no abortion in 3 hours another 200 μg
Follow up	day 8 – 15	day 10 – 18

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Pivotal Studies

	Study I	Study II	Total
Total no. women enrolled	1286	1194	2480
No. women with gestation ≤ 49 days	1189	492	1681
No. women with gestation ≥ 50 days	16	612	628

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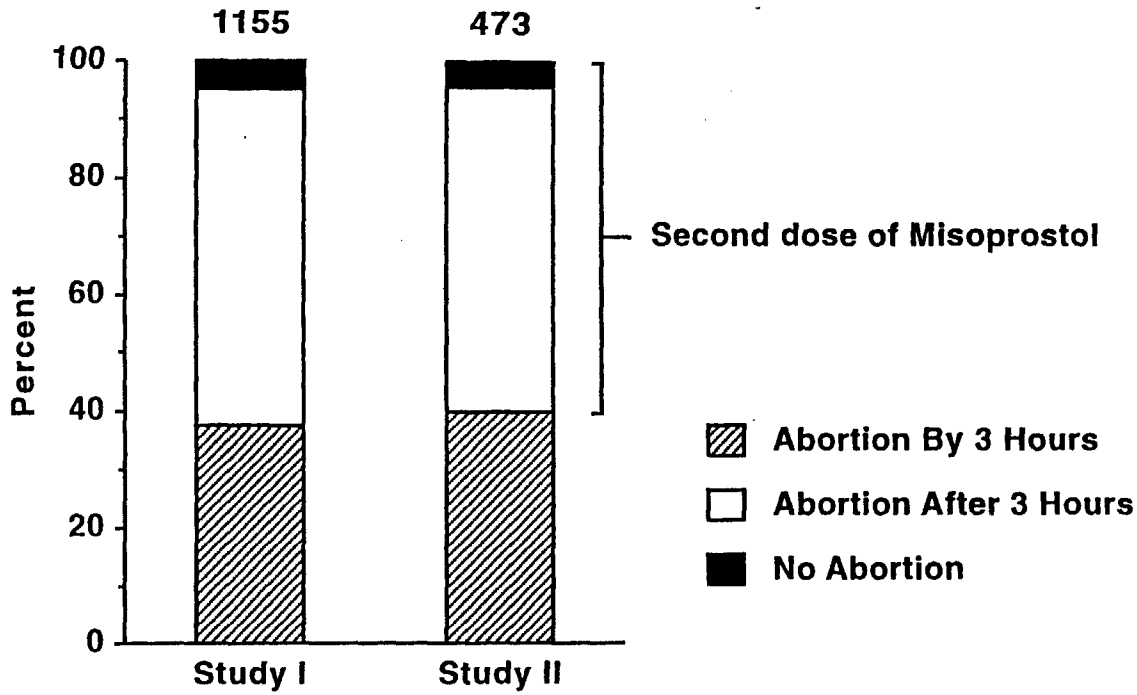
Outcome Analysis of Women Who Received Misoprostol
Duration of Gestation ≤ 49 Days



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Pivotal Studies:
Complete Medical Termination of Pregnancy:
Duration of Gestation ≤ 49 Days

- **Total evaluated: 1681**
- **Complete medical abortion: 95.5%**

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Pivotal Studies:
Failure of Medical Termination of Pregnancy:
Duration of Gestation ≤ 49 Days

- Total evaluated: 1681
- Continuing pregnancy: 1.3%
- Incomplete abortion: 2.9%
- D & C / VA for bleeding: 0.3%

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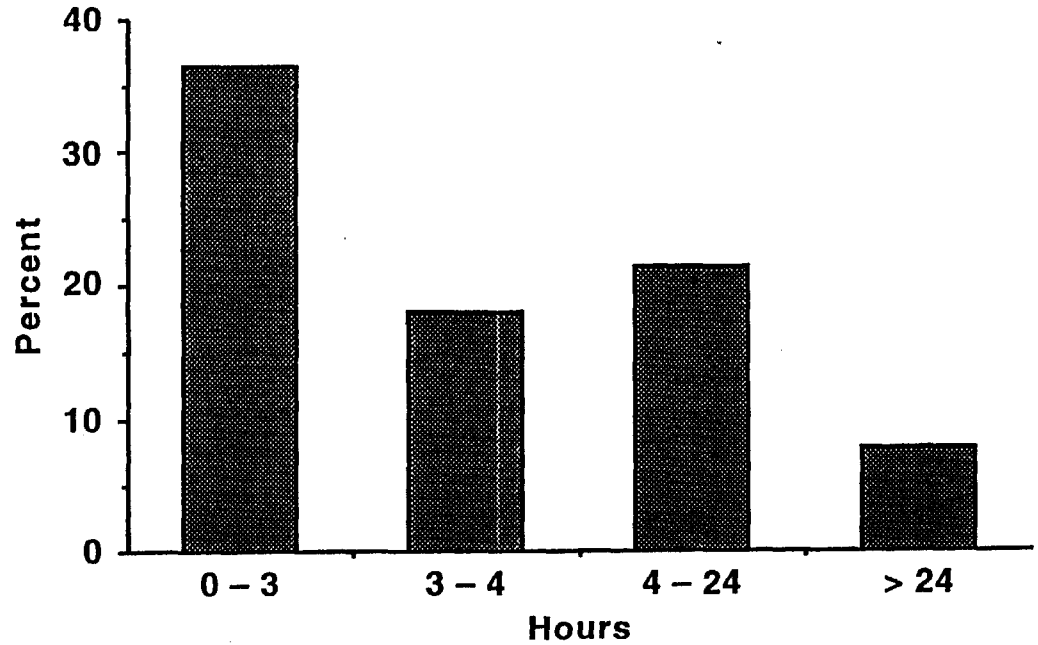
Time of Expulsion After Misoprostol
Duration of Gestation ≤ 49 Days



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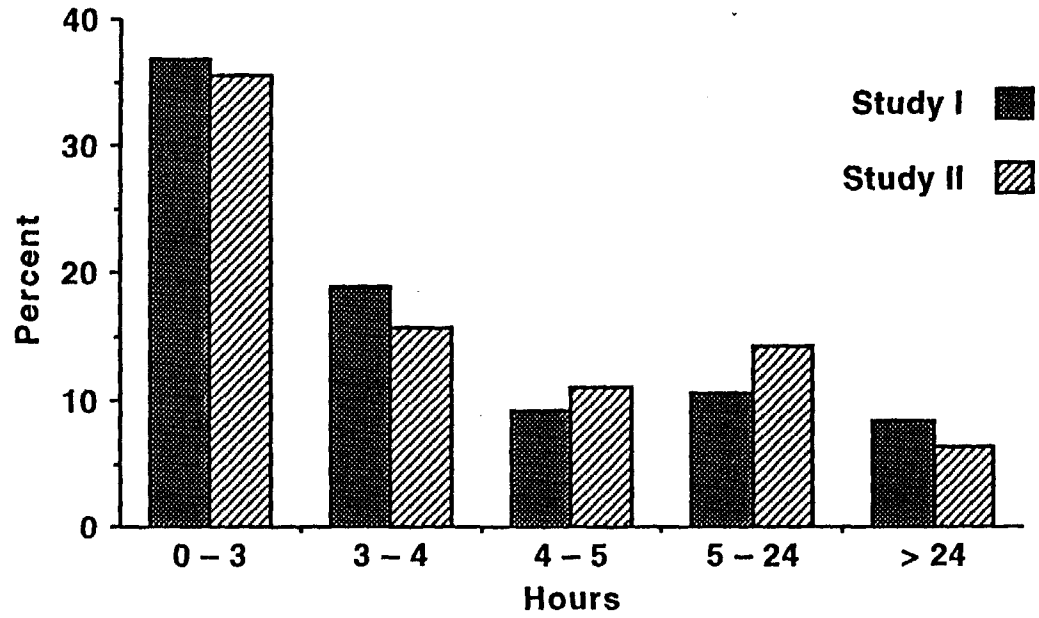
Time of Expulsion
Effect of a Second Dose of Misoprostol
Duration of Gestation ≤ 49 Days



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Patient Characteristics Evaluated

- age
- height
- weight
- body mass index
- gravity
- parity
- number of previous abortions
- duration of gestation

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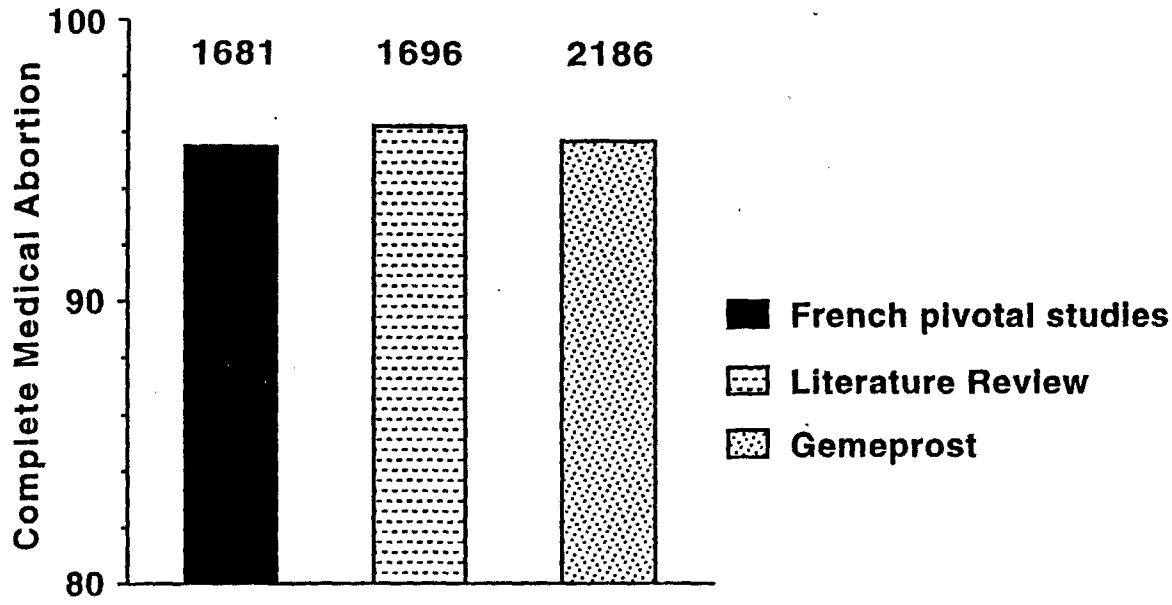
Summary of Efficacy

Duration of Gestation ≤ 49 Days



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Conclusion

It is concluded that Mifepristone plus Misoprostol is effective for the medical termination of pregnancy in women with duration of gestation of 49 days or less.

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History of the Use of Mifepristone Plus Misoprostol for Medical Abortion

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Developmental Milestones in the Marketing of Mifepristone for Pregnancy Termination

1970 — Identification of the progesterone receptor (PR)

1982 — Initial report of medical termination of pregnancy with mifepristone, the first PR antagonist.

1983 — The Population Council files IND for clinical trials of mifepristone in the the U.S.

1988 — Marketing approval in France and China

1991 — Marketing approval in the United Kingdom

1992 — Marketing approval in Sweden

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Clinical Development of Mifepristone

- Initial report of pregnancy termination with mifepristone
- Selection of a single 600 mg dose of mifepristone
- The addition of a prostaglandin increases efficacy
- Demonstration of serious adverse events with sulprostone
- Clinical trials with mifepristone and misoprostol in France

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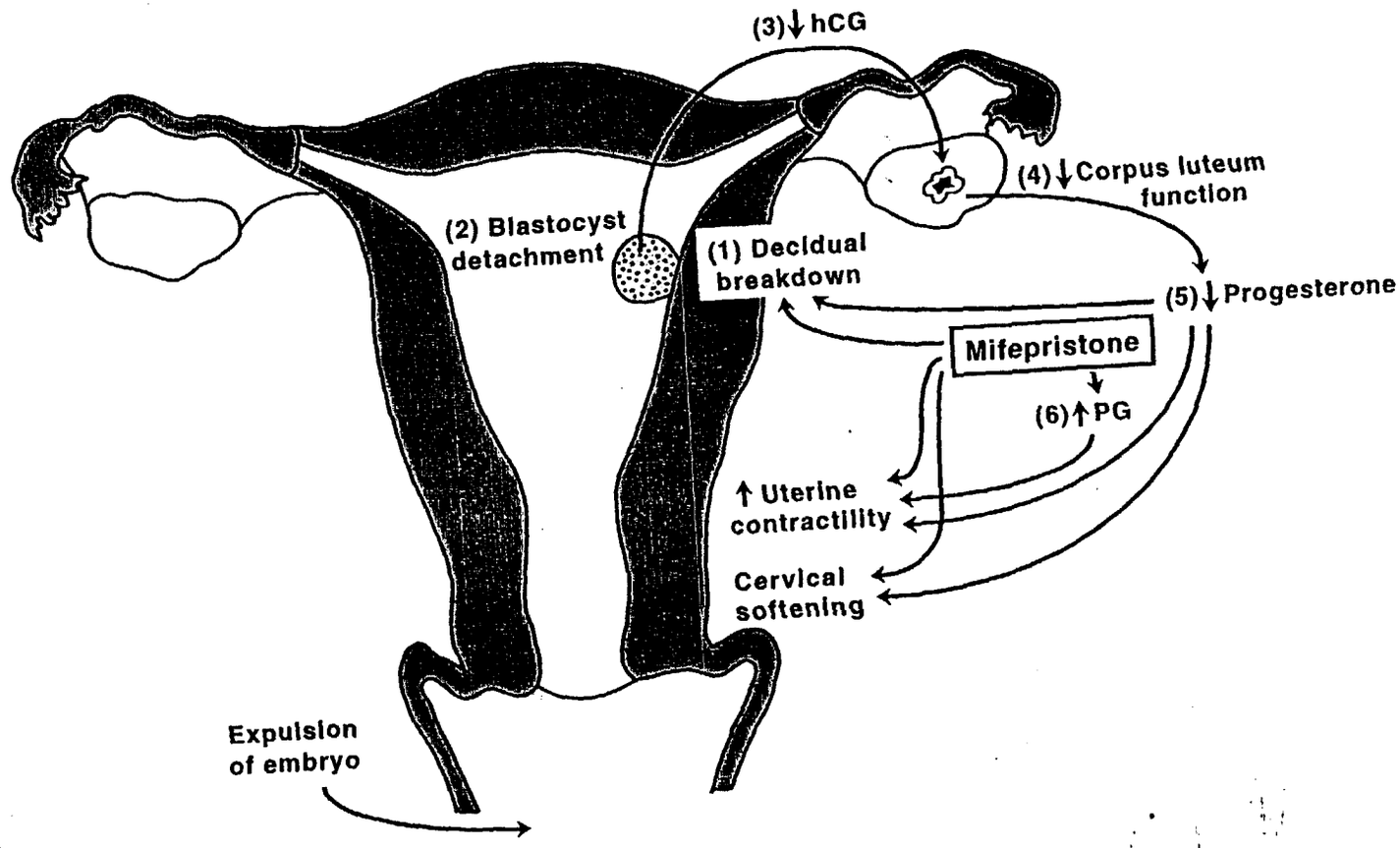

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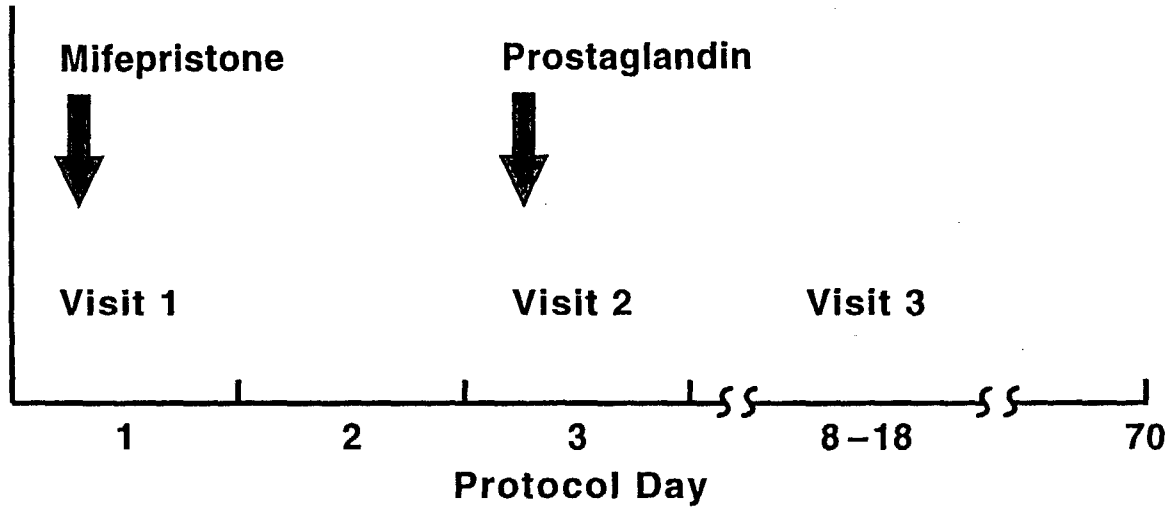

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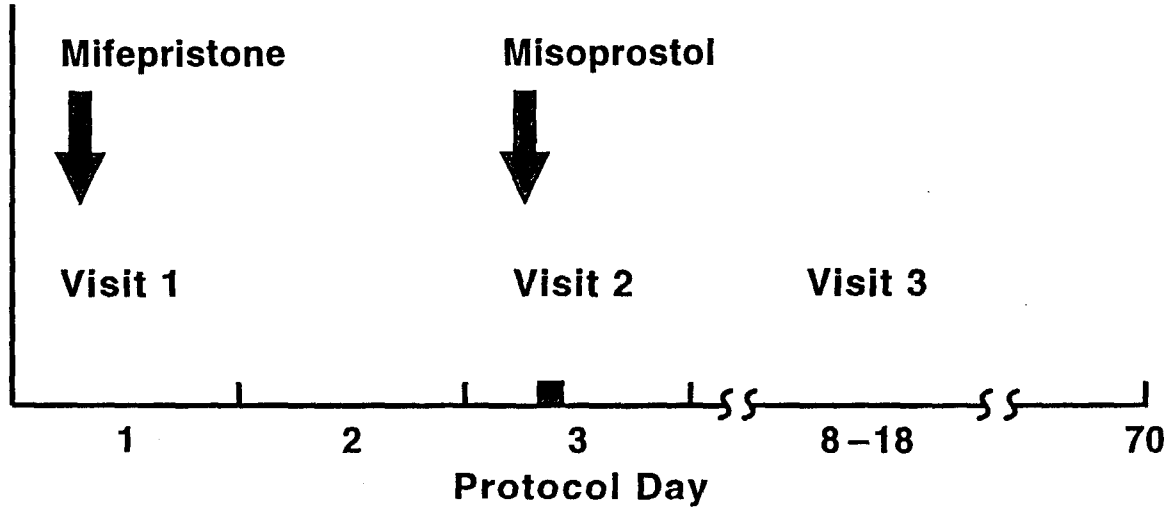
French Studies of Mifepristone and Misoprostol



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Registration of Mifepristone in the U.S. by The Population Council

May 1994: • The Population Council is granted U.S. rights for the use of Mifepristone

U.S. Clinical Trial

New Drug Application

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Registration of Mifepristone in the U.S. by The Population Council

U.S. Clinical Trial

- Initiated Fall 1994
- 2121 women enrolled
- ≤ 63 days of gestation
- 17 clinical sites
  - — geographically distributed
  - — variety of provider settings

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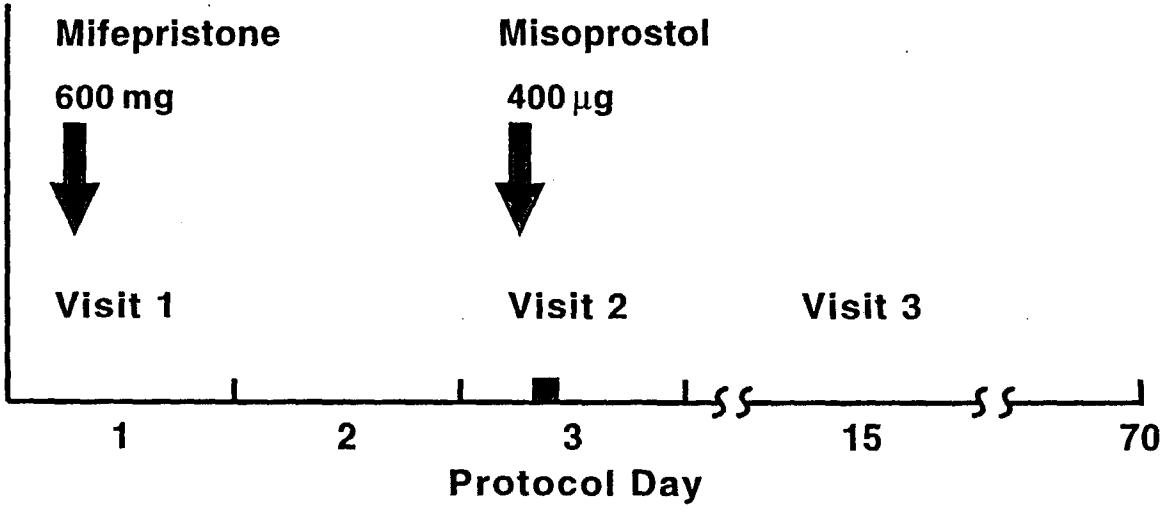
U.S. Clinical Trial



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Registration of Mifepristone in the U.S. by The Population Council

New Drug Application

Summer 1994:	• Pre-NDA meeting with the FDA • NDA preparations begin
Fall-Winter 1994:	• Obtain database for French trials • Audit/validation of the database • Full re-analysis of the French database
Summer 1995:	• Cut-off date for information to be included in the NDA
Fall-Winter 1995:	• Final production of NDA begins
Spring 1996:	• NDA submitted to the FDA
Summer 1996:	• FDA audits French pivotal trial sites and data

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Clinical Features of the NDA

- Background: efficacy and safety data
  - — mifepristone alone
  - — mifepristone + other prostaglandins
- Pivotal trials: efficacy and safety data
  - — mifepristone + misoprostol
  - — two French studies
  - — 2480 subjects
- International safety data
  - — other clinical trials
  - — compassionate use
  - — post-marketing surveillance

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Advisory Committee for Reproductive Health Drugs
July 19, 1996

Non-U.S. Clinical Studies

Ridgely C. Bennett, M.D., M.P.H.
Medical Officer, DRUDP

Proposed Regimen

- Single oral dose of three 200 mg tablets of mifepristone
- In two days, two 200 ug tablets of misoprostol, unless confirmed termination

Studies 14 and 24: Design

	Study 14	Study 24
No. patients	1286	1194
Duration of gestation	$\leq$ 49 d	$\leq$ 63 d
Day 1: Mifepristone	600 mg	600 mg
Day 3: Misoprostol	400μg	400 μg; if no abortion in 3 hours, additional 200 μg
Follow-up	Day 8-15	Day 10-18

Exclusion Criteria

- Smoke $\geq$ 10 cigarettes/day
- Cardiovascular disease
- Asthma
- Glaucoma or high intraocular pressure
- Diabetes
- Hyperlipidemia
- Renal, adrenal, or hepatic insufficiency
- Anemia

Treatment Outcome: Definition

- **Successful: complete expulsion without need for surgery**

- **Failure:**
  - **incomplete expulsion**
  - **pregnancy continued**
  - **surgery required for hemostasis**

Efficacy Evaluable Population

- **Pregnancy confirmed**

	n/N	%
Study 14	1205/1286	93.7
Study 24	1104/1194	92.5

Study 14: Treatment Outcome

Efficacy Evaluable Population

	N	Rate (%)
Complete expulsion	1149	95.4
Incomplete expulsion	34	2.8
Ongoing Pregnancy	18	1.5
Surgery to stop bleeding	4	0.3
Total	1205	