MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Lewis
Former Member of the
Advisory Committee for Reproductive Health Drugs

With this FAX, we want to notify you that today the Food and Drug Administration approved the new drug application for Mifeprex (mifepristone).

Because you participated in providing advice to the Agency on this product and because the approval of this product is very controversial we want to inform you in as timely a manner as possible of our action.

We have attached the FDA press release announcing the decision. As you will see, an Agency telephone number is available at which Agency personnel can be reached to answer telephone calls from the public regarding the Agency's action on the product. That telephone number is: **1-888-463-6332**. Alternatively, you may call our office (**301-827-7001**) if you have questions and we will forward them on to the appropriate person within the Agency.

As also indicated in the press release, we have created a web site which we believe will answer most questions regarding the product. The web site can be found at: **http://www.fda.gov/cder/drug/infopage/mifepristone**

Attachment

APPEARS THIS WAY
ON ORIGINAL

P00-19
September 28, 2000
FOR IMMEDIATE RELEASE

FOOD AND DRUG ADMINISTRATION
Print Media: 301-827-6250
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

FDA APPROVES MIFEPRISTONE FOR THE TERMINATION OF EARLY PREGNANCY

The Food and Drug Administration today approved mifepristone (trade name Mifeprex) for the termination of early pregnancy, defined as 49 days or less, counting from the beginning of the last menstrual period.

Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin. Women will return for a follow-up visit approximately 14 days after taking mifepristone to determine whether the pregnancy has been terminated.

Because of the importance of adhering to this treatment regimen, each woman receiving mifepristone will be given a Medication Guide that clearly explains how to take the drug, who should avoid taking it, and what side

-More-

effects can occur.

"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

FDA based its approval of mifepristone on data from clinical trials in the United States and France.

The labeling for mifepristone emphasizes that most women using the product will experience some side effects, primarily cramping and bleeding. Bleeding and spotting typically last for between 9 and 16 days. In about one of 100 women, bleeding can be so heavy that a surgical procedure will be required to stop the bleeding.

The drug's labeling also warns that it should not be used in women with the following conditions:

- Confirmed or suspected ectopic ("tubal") pregnancies
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To gather additional data about the use of mifepristone, the Population Council (sponsor of the product) has made a commitment to conduct postmarketing studies. These include a study comparing patient outcomes among physicians who refer their patients needing surgical intervention, compared to those who perform surgical procedures themselves; an audit of prescribers that will examine whether patients and their physicians are signing the patient agreement and placing it in the patient's

medical record, as required; and a system for surveillance, reporting and tracking rare ongoing pregnancies after treatment with mifepristone in the U.S.

Mifepristone, which was developed by a French pharmaceutical firm, was first approved for use in France in 1988. Since then, more than 620,000 European women have taken mifepristone in combination with a prostaglandin to terminate pregnancy. The drug has also been approved in the United Kingdom, Sweden, and other countries.

Mifepristone will be distributed in the U.S. by Danco Laboratories, LLC, New York, N.Y.

More detailed information about this product is available on FDA's website at http://www.fda.gov/cder/drug/infopage/mifepristone/

####

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Cassandra Henderson

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. HENDERSON.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

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Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Henderson
Former Member of the
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"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

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CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Ricardo Azziz

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. AZZIZ.

THANK-YOU

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

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FDA based its approval of mifepristone on data from clinical trials in the United States and France.

The labeling for mifepristone emphasizes that most women using the product will experience some side effects, primarily cramping and bleeding. Bleeding and spotting typically last for between 9 and 16 days. In about one of 100 women, bleeding can be so heavy that a surgical procedure will be required to stop the bleeding.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Thomas S. Kosasa

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. KOSASA

THANK-YOU

APPEARS THIS WAY
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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Kosasa
Former Member of the
Advisory Committee for Reproductive Health Drugs

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effects can occur.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Diana B. Petitti

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO Dr. PETITTI.

THANK-YOU

APPEARS THIS WAY
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[redacted]

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Department of Health and Human Services
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Former Member of the
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ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Mary Jo O'Sullivan

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. O'SULLIVAN

THANK-YOU

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Food and Drug Administration
Center for Drug Evaluation and Research

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"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

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####

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Jane Zones

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. ZONES.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Jones
Former Member of the
Advisory Committee for Reproductive Health Drugs

With this FAX, we want to notify you that today the Food and Drug Administration approved the new drug application for Mifeprex (mifepristone).

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P00-19
September 28, 2000
FOR IMMEDIATE RELEASE

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####

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Janet Daling

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. DALING.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Daling
Former Member of the
Advisory Committee for Reproductive Health Drugs

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effects can occur.

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####

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Mary Hammond

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. HAMMOND.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Hammond
Member of the Advisory Committee for Reproductive Health Drugs

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CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Kenneth Ryan

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #:

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. RYAN

THANK-YOU

10/6/00
Dr. Ryan,
I want to follow up my telephone call & the FAX that I sent out to the past Repro Drug Adv. Comm. members last week. Thanks for getting back to me.
/s/

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Ryan
Former Member of the
Advisory Committee for Reproductive Health Drugs

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####

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: ——————— (HFD-715) /S/ 9/27/00

THROUGH: ——————— (HFD-715) /S/ 9/27/00

TO: NDA 20-687 (HFD-580)

SUBJECT: Efficacy of Mifepristone by age, submission dated September 12, 2000

My previous review of "efficacy of mifepristone by age" includes an evaluation of the results reported by Spitz et. al[1]. I concluded the Spitz et al article cannot be used to determine if the success rate is unrelated to age, because a test of this relationship was not reported in the article.

In response, the applicant has now submitted an analysis to support the conclusion in the article by Spitz et al that outcomes are unrelated to age. This submission contains a chi-square test of independence between efficacy of mifepristone and age in the U.S. clinical trials, and the underlying contingency table used for the test.

My evaluation of this information concludes the success rate decreases as age increases. This conclusion disagrees with the applicant's conclusion that outcomes are unrelated to age. This disagreement is due to the handling of age in the analyses. My analyses consider age as an ordinal variable; the applicant's analyses consider age a nominal variable.

New analysis of the relationship between efficacy and age:
The age groupings differ from those reported in the clinical study reports. Whereas, the study reports break age into 5 categories, this submission combines the two youngest age categories into a single category (see Table 1).

Using a Pearson chi-square test, the applicant reports a p-value of 0.222. This result leads to their conclusion that age and outcome are unrelated.

APPEARS THIS WAY
ON ORIGINAL

[1] IM Spitz, CW Bardin, L Benton, A Robbins; "Early pregnancy termination with mifepristone and misoprostol in the United States," New England Journal of Medicine, 1998.

Table 1. Summary of Success Rates by Age Category – Spitz et. al

Age (years)	N	Rate of success
<25	290	93.8%
25-29	251	93.2
30-34	180	90.0
>35	106	88.7
Total	827	92.1

Source of data: submission dated September 12, 2000

Unlike the Pearson chi-square reported by the applicant, my analyses take advantage of the ordering of the age categories. I analyzed the effect of age on the efficacy of mifepristone by several methods:

1. Logistic regression with success rate as the dependent variable and age as a predictor, where age was coded as either 1, 2, 3, 4, or 5.
2. Logistic regression with success rate as the dependent variable and age as a predictor, where age was coded as the mid-point of the age categories: 20.5, 27, 32, or 37.
3. Linear regression with success rate as the dependent variables and age as a predictor, where age was coded as the mid-point of the age categories.

In each case, the results indicate efficacy decreases with increasing age with a p-value of approximately .05. This p-value is somewhat higher than the 0.03 reported in my earlier review. This is due to combining the two youngest age categories.

When the two youngest age categories (<20 years and 20-24 years) are combined, an observed increase in success rate among the youngest women is obscured:

Table 2. Summary of Success Rates by Age Category

Age (years)	N	Rate of success
<20	57	98.2%
20-24	233	92.7
25-29	251	93.2
30-34	180	90.0
>35	106	88.7

Source of data: NDA

Reviewer's conclusion
My conclusion is the efficacy of mifepristone decreases as age increases.

Archival NDA 20-687
HFD-580

Per discussion, this package contains the following:

1. Draft approval letter
2. Most recent labeling (text for the package insert) and the Medication Guide
3. [redacted]
4. All clinical reviews
5. Most recent statistical review
6. Most recent biopharm review
7. Most recent chemistry review
8. Report on the facility inspections
9. Most recent pharm/tox review
10. Meeting minutes from the current review cycle

There is a meeting with the Pop Council at 11 am on 9/15. If there are major changes to any of the above, we'll fax them to you.

/S/

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

SEP 15 2000

Date: September 15, 2000

From: [redacted] Clinical Pharmacology and Biopharmaceutics Reviewer, HFD-870

/S/ 9/15/00

Through: [redacted] Clinical Pharmacology and Biopharmaceutics Team Leader, HFD-870

/S/ 9/15/00

To: HFD-580

Re: NDA 20-687 Labeling

At the time of the original review, [redacted] of the Clinical Pharmacology section, the statement 'drugs known to cause enzyme induction may reduce the efficacy of mifepristone due to increased metabolism' was removed from the sponsor's label since there was no information on the pathways/enzymes responsible for metabolism of mifepristone. However, since the time of the original review, information regarding the isozymes responsible for the *in vitro* metabolism of mifepristone has been published in literature articles[1]. Therefore, upon review of the current literature information, the following recommendations are made to the Clinical Pharmacology section of the sponsor's proposed labeling. These recommendations were agreed upon by the sponsor and were appropriately incorporated into the final labeling.

Distribution

In the first sentence, the word [redacted] should be changed as 'α_1-acid glycoprotein'.

Add 'with a terminal elimination half-life of 18 hours' to the end of last sentence of this section.

Metabolism

This section should be revised as follows:

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are as follows: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Drug Interactions

This section should be revised as follows:

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's wort and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interactions may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

[1]Literature articles reviewed for the information on the metabolism of mifepristone:

1). Jang GR, Wrighton SA, and Benet LZ; Biochem Pharmacol 1996 Sep 13; 52 (5):753-61
2). Heikinheimo O; Clin Pharmacokinet 1997 Jul; 33(1):7-17
3). Jang GR and Benet LZ; Pharmacology 1998 Mar: 56(3):150-157
4). Jang GR and Benet LZ; J Pharmacokinet Biopharm 1997 Dec; 25(6): 647-672

SEP 15 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: _____ (HFD-715) /S/ 9/15/00

THROUGH: _____ (HFD-715) /S/ 9/18/00

TO: NDA 20-687 (HFD-580)

SUBJECT: Efficacy of Mifepristone by age

This memo reports my

(a) analyses and results of whether age is related to the efficacy of mifepristone,
(b) assessment of the results reported by Spitz et. al.[1]: "...[efficacy] outcomes were unrelated to ... base-line characteristics, including age ...".

I analyzed the effect of age on the efficacy of mifepristone by several methods. In each case, the results indicate efficacy decreases with increasing age.

The article by Spitz et. al. does not include enough information to support the applicant's assertion that age and outcome are unrelated.

The details follow.

Analyses of the relationship between efficacy and age

The two U.S. studies (166A and 166B) were combined; these data were used for the analyses:

Table. Summary of Success Rates by Age Category

Age (years)	N	Rate of success
<20	57	98.2%
20-24	233	92.7
25-29	251	93.2
30-34	180	90.0
>35	106	88.7
Total	827	92.1

Source of data: NDA

[1] IM Spitz, CW Bardin, L Benton, A Robbins; "Early pregnancy termination with mifepristone and misoprostol in the United States," New England Journal of Medicine, 1998.

The following analyses were done:

1. Logistic regression with success rate as the dependent variable and age as a predictor, where age was coded as either 1, 2, 3, 4, or 5.
2. Logistic regression with success rate as the dependent variable and age as a predictor, where age was coded as the mid-point of the age categories: 18.5, 22, 27, 32, or 37.
3. Linear regression with success rate as the dependent variables and age as a predictor, where age was coded as the mid-point of the age categories.
4. A chi-square test for slope[2].

Each analysis shows the success rate decreases as age increases. In each case, the p-value is approximately .03.

Spitz et. al.

The applicant incorrectly interprets the results of this study when they say efficacy is not related to age. A correct interpretation is "after adjusting for gestational age and number of previous elective abortions, no other baseline characteristics were significantly related to success or failure."

The article does not report a test of whether success or failure is related to age. Therefore, the reported results cannot be used to assess the relationship between outcome and only age.

Instead of specifically testing the relationship between age and outcome, the authors use a *forward* step-wise logistic regression[3] to evaluate the relation between success or failure, and various baseline patient characteristics. The analysis explores which baseline characteristic[4], or combination of characteristics, is the most highly related to success or failure.

A stepwise procedure is iterative:

1. The procedure selects the variable most highly related to outcome.
2. That variable enters the model.
3. From the remaining variables, the procedure selects the variable most highly related to outcome after adjustment for the variable(s) already in the model.
4. That variable enters the model.

This iterative procedure continues until no variable is statistically related to the outcome after adjusting for variables in the model.

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[2] see pages 143-146 in JL Fleiss, Statistical Methods for Rates and Proportions, Second Edition, John Wiley & Sons, New York, 1981.

[3] The authors appeared to have used a model that allowed a variable to exit if the significance value was greater than 0.10. This aspect of the model does not appear to have had an effect on the results, and will not be discussed further.

[4] The baseline characteristics considered were gestational age, number of previous elective abortions, age, race, body weight, gravidity, and previous spontaneous abortions.

The step-wise procedure identified two variables related to outcome: gestational age and the number of previous elective abortions. After these variables were in the model, no other variable was statistically related to outcome.

Reviewer's conclusions

1. From my analyses of the data in the U.S. studies, the success rate decreases as age increases.
2. The Spitz et al article cannot be used to determine if the success rate is related to age, because a test of this relationship was not done.

Archival NDA 20-687
HFD-580
HFD-715/Division files

APPEARS THIS WAY
ON ORIGINAL

SEP 1 4 2000

9/14/00
discussed

NDA 20-687
Mifepristone

9/14/00

Pharmcology Team Leader Labeling Memo #3

Under the Overdosage section, the term ——— should be replaced with "oral acute lethal dose".

/S/

9/14

NDA 20-687
HFD-580

- phase 4
- medguide
- Support H
- labeling / PA / PhA

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Date: 18 Feb. 2000

From: [redacted] /S/ 19 Feb 2000
[redacted] Office of Drug Evaluation III

To: [redacted]
[redacted] Office of Drug Evaluation III /S/ 2/25/00

Cc: [redacted] HFD-580
[redacted] HFD-580

Subject: NDA 20-687
Trade name not specified, 200 mg tablet
Mifepristone, (11ß, 17ß)-11-[(4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)-estra-4, 9-dien-3-one.
Review of Pharm./Tox. Comments and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 20-687, 22 Jul. 1996, written by [redacted]
2. NDA 20-687 'Approvable' Package, with Draft Product Labeling (draft dated 3 Sept. 1999).

II. Comments and Conclusions

1. A review of the action package for NDA 20-687 (mifepristone) suggests that the product has been adequately evaluated in multiple non-clinical safety studies (including reproduction, genotoxicity, safety pharmacology, and acute and repeat dose toxicology studies up to 26 weeks duration) for potential approval as an agent for the medical termination of intrauterine pregnancy through 49 days of pregnancy.

3. The draft labeling for mifepristone suggests that teratogenicity studies could not be conducted because of the abortifacient properties of the drug. However, the NDA review includes descriptions of multiple teratology studies conducted in the rat and rabbit. While drug exposure in these studies was small (approx. 3 and 10% of the human dose based on body surface area [rat and rabbit, respectively]), the designs were adequate and fetal survival was demonstrated. Minimal evidence of adverse fetal effects was apparent in either species (i.e., delays in ossification) when an abortion was not induced by mifepristone administration. It is suggested that the pregnancy section of the label be

revised to include a discussion of the non-clinical teratology studies conducted with mifepristone, the low multiplicity of human exposure and the adverse fetal effects observed.

5. A summary of recommended changes to the carcinogenesis, mutagenesis, fertility and pregnancy sections of the proposed product labeling are presented below.

   - It is recommended that all interspecies dose comparisons included in the product label be based on pharmacokinetic parameters (i.e., AUC, C_{max} or other relevant parameter) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling or nominal dose), or there is insufficient pharmacokinetic data to allow for interspecies dose comparisons.
   - It is recommended that the genotoxicity studies described in the proposed product label under the heading of "Carcinogenesis, Mutagenesis, Impairment of Fertility", be clearly identified as having been conducted "in vitro" or "in vivo" as is appropriate for each study methodology.
   - A description of the effects of mifepristone on in utero fetal development should be included in the product label.

6. If data are available, consideration should be given to the inclusion of information on breast milk drug concentration and neo-natal drug exposure in woman taking mifepristone during lactation.

III. Summary

A review of the action package for NDA 20-687 (mifepristone) suggests that the product has been adequately evaluated in multiple non-clinical safety studies (including reproduction, genotoxicity, safety pharmacology, and acute and repeat dose toxicology studies up to 26 weeks duration), for potential approval as an agent for the medical termination of intrauterine pregnancy through 49 days of pregnancy.

Potential revisions to the proposed product label for mifepristone are presented in the preceding section of this document.

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[1] The current Pregnancy categories may not adequately address the classification of a product such as mifepristone, which is specifically intended for use in the termination of a pregnancy. The Division and Office may wish to omit the Pregnancy Category from the label for mifepristone, substituting instead a description of the product indication (i.e., "Mifepristone is indicated for use in the termination of pregnancy (prior to day 49 of pregnancy), and has no other approved indication for use during pregnancy.").

FEB 17 2000

Memo
New Drug Application

NDA: 20-687

Sponsor: Population Council, Inc.

Drug: [Tradename] (mifepristone) 200mg tablet for oral administration

Indication: Termination of intrauterine pregnancy up to 49 days since Last Menstrual Period (LMP)

Date received: Original NDA: March 18, 1996
Approvable letter issued: September 18, 1996
Complete Response received: August 18, 1999

Date of Memo: February 17, 2000

In this complete response to the approvable letter issued in September 1996, the applicant has presented further information in support of the use of mifepristone for the termination of pregnancy from diagnosis and up to seven weeks (49 days) of amenorrhea. In this setting mifepristone is ingested orally as three 200mg tablets followed 48 hours later by two 200ug tablets of misoprostol.

Clinical/Statistical

Results from several studies to establish the safety and efficacy of mifepristone plus misoprostol were reviewed as a result of the application submitted March 18, 1996. The two "pivotal" trials, both conducted in France, included in this original application revealed a complete abortion rate of 95% (for intrauterine pregnancies ≤ 49 days since last menstrual period—LMP). Although preliminary results from a large US trial were submitted for review with the original 1996 application, the current resubmission contains the final study report for this US trial.

The trial results are extensively described and analyzed in the Medical Officer review. Of the 2,121 women enrolled in the US, 859 were in the ≤ 49 days amenorrhea group. Efficacy was 92% in this group. Effectiveness was less beyond 49 days of amenorrhea. The original French studies reported an average duration of bleeding of 9 days. For the US studies this average was 14 days. Adverse event reporting was higher in the US population as compared to the French results but remained acceptable. The most common adverse event reported was abdominal cramping—an expected outcome. In the ≤ 49 days amenorrhea group, excessive bleeding led to transfusion in one US patient and an additional 2 women were treated in the emergency setting for excessive bleeding. The MO review describes data in comparison to surgical abortion. In the end, I agree with the MO conclusion that mifepristone plus misoprostol as described in the clinical studies is effective for termination of pregnancies up to 49 days since LMP and has an acceptable safety profile.

Clinical Audits

In 1996, two French sites were audited and found acceptable. For this review cycle, three US sites were selected by the review team and were audited by the Division of Scientific Investigations. All three (sites in California, Washington and Iowa) were found acceptable.

Clinical Pharmacology and Biopharmaceutics

The outstanding question of appropriate dissolution specifications has been considered. The chemists and the Office of Clinical Pharmacology and Biopharmaceutics have described revised specifications. These specifications will be conveyed in the action letter.

Pharmacology/Toxicology

Adequate non-human studies have been performed and found acceptable. Labeling comments will be included in the action letter.

Chemistry

Our September 18, 1996 requests that the sponsor apply to USAN for an established name. The March 1997 correspondence from the sponsor indicates that they did not understand this request as they refer to determining a "tradename" rather than applying for an established name. In a further correspondence dated June 25, 1999 the applicant has indicated that they have obtained approval of the USAN council for adoption of the name, mifepristone.

The proposed tradename "Mifeprex" was found to not be acceptable by the Office of Post-marketing Drug Risk Assessment. The alternative name proposed ——— was found to be acceptable at this time.

As the chemistry reviews describe, several outstanding questions remain regarding both drug substance and drug product. Also, the drug substance manufacturing site has failed GMP inspection. Resolution of the chemistry and inspection issues will be required prior to an approval action.

Advisory Committee Activities

The Reproductive Health Drugs Advisory Committee met in July 1996 to consider this application and recommended approval. The committee expressed interest in seeing the final US study report as well as final labeling. The US study results, as published in an April 30, 1998 issue of the New England Journal of Medicine, were sent to the members of the Advisory Committee on November 1, 1999. No specific comments were received from this mailing.

Final labeling will be sent to the Advisory Committe members on approval of this application.

Labeling—prescription and patient

Our September 18, 1996 approvable letter requires submission of revised labeling. The sponsor has responded to these labeling requests in correspondence dated March 28, 1998 and again on June 25, 1999. The review team, along with the Division of Drug Marketing, Advertising and Communication have addressed the proposed labeling during this review cycle. All team comments have been collated and discussed. Our recommendations for labeling changes are provided in a "strike-out/underline" version and will be conveyed with the action letter. Major areas for consideration include:

1. We recommend that the labeling include a black boxed warning describing the major requirements and conditions for use.
2. The sponsor has proposed that the medication given on day 2 of the regimen (misoprostol) could be given either in the office/clinic (as per the clinical trials) or at home. The Division and Office have

discussed this proposal and find it acceptable. No changes in safety or efficacy are expected based on the location of ingestion of the misoprostol.

3. DDMAC has provided extensive comments regarding the patient labeling including the proposed "acknowledgement" section.

Distribution System and Subpart H recommendations

Under 21CFR 314 Subpart H, the agency can determine that a drug can be approved with restrictions to assure safe use. We have concluded that mifepristone is a candidate for Subpart H 314.520 when and if the product is approved. 314.520 states:

a If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:
   1 Distribution restricted to certain facilities or physicians with special training or experience; or
   2 Distribution conditioned on the performance of specified medical procedures.

b The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

The sponsor submitted a distribution plan proposal in January 2000. After consideration of their proposal, we have concluded that the Subpart H provisions are appropriate for approval of this product. The distribution plan will need to be revised to include adequate training and certification of providers. The labeling and training materials will need to include information on reporting of events to both the sponsor and to the FDA. The distribution system will need to include a quality assurance/quality control component. As the system is developed, we can work with the applicant in order to incorporate a data collection component for the various Phase 4 commitments listed below.

Subpart H approval will also allow the FDA to impose similar distribution restrictions and system on any future generic mifepristone approved for this indication.

Phase 4 Commitments

The approvable letter of September 1996 describes six areas of commitment made by the applicant for Phase 4 study. In this complete response of August 1999, the applicant addresses each commitment and proposes approaches to each of the commitments made. These commitments will again need to be included in the current action letter. The commitments include:

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 (a) less than 18 years of age, (b) over age 35 and (c) who smoke.
6. To ascertain the effect of the regimen on children born after treatment failure.

Other Petitions/Correspondence

A letter dated June 21, 1999 was sent to [redacted] Center for Drug Evaluation and Research (CDER), requesting a discussion of confidentiality issues for the drug substance

and product manufacturers. This letter was followed by a July 14, 1999 correspondence addressed to [redacted] Office of Training and Communication (OTCOM), providing further discussion of the confidentiality concern. A subsequent correspondence was received in January, 2000. The confidentiality issues are under review by the Office of Chief Counsel. Along with the request for manufacturer confidentiality, the Division of Reproductive and Urologic Drug Products also sent a request to the Office of Chief Counsel for consideration of reviewer confidentiality after approval.

Recommendations

Approval of this regimen is recommended once chemistry issues are adequately resolved and appropriate labeling and distribution system is in place.

/S/ 2/17/00

[redacted] Division of Reproductive and Urologic Drug Products

cc: NDA 20-687
HFD-580/ [redacted]
HFD-103/ [redacted]

APPEARS THIS WAY
ON ORIGINAL

SEP 1 4 2000

Memorandum

Subject: Complete response dated March 31, 2000
to approvable action on Feb. 18, 2000
Received: NDA 20-687
Date of Memorandum: 9/14/00
Indication: Medical termination of intrauterine pregnancy through 49 days of pregnancy
Drug: Mifepristone
Pharmacologic Class: Antiprogestational Agent
Dose: Three 200 mg tablets of mifepristone orally.
If termination of pregnancy has not occurred by day three, two 200 μg tablets of misoprostol are administered.
Sponsor: Population Council

Background

Mifepristone is a synthetic steroid that competitively inhibits the activity of progesterone. When it is used in combination with misoprostol, a prostaglandin analog, it results in termination of pregnancy.

The initial NDA was submitted on March 18,1996 and was granted priority review status. The sponsor submitted data from two trials completed in France and preliminary data from a large US study. In July 1996, The Reproductive Health Drugs Advisory Committee met to discuss the application. The Advisory Committee voted for approval with major recommendations regarding labeling, phase 4 commitments and restricted distribution. FDA agreed with the recommendations of the Advisory Committee and issued an approvable letter on Sept. 18, 1996, which specified the requirements for approval. Besides the clinical issues, there were significant chemistry and manufacturing deficiencies, which had to be addressed.

The response to the approvable letter was submitted by the sponsor on August 18, 1999 and included the final results of the US study. In this study of the 859 subjects with less than 49 days of amenorrhea, 92% had successful termination of pregnancy. There was a lower rate of efficacy beyond 49 days. The Division concluded that the drug regimen including mifepristone and misoprostol is safe and effective until 49 days of pregnancy as dated from the first day of the last menstrual cycle in a presumed 28-day cycle. However, CMC issues were not resolved and the drug substance manufacturing site failed inspection. During this review, The Division determined that 21 CFR 314.520 Subpart H applies to this application and that the drug can only be used safely with restricted distribution. On February 18, 2000, a second approvable letter was issued stating the issues that had to be addressed prior to approval. The major outstanding issues related to approvability of this drug are summarized as follows:

CMC issues related to drug substance, drug product and requirement for acceptable GMP inspection.

Phase 4 commitments

1. Monitor the adequacy of the distribution and credentialing system;

2. Follow the outcome of a representative sample of women who have surgical abortion because of method failure;

3. Access the long term effects of multiple uses of the regimen;

4. Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not;

5. Study the safety and efficacy of the regimen in women under 18, over 35 and those who smoke; and

6. Ascertain the effect of the regimen on children born after treatment failure.

Acceptable Distribution Plan under 21 CFR 314.520 Subpart H

The Agency determined that the termination of an unwanted pregnancy is a "serious" condition under Subpart H and that that there is "meaningful therapeutic benefit" over existing surgical abortion because there is avoidance of a surgical procedure. In addition, the Agency has concluded that this product can only be used safely if the distribution is "restricted to certain facilities or physicians with special training or experience"

In the case of mifepristone, the Agency has determined that distribution should be limited to physicians who can date the pregnancy and diagnose ectopic pregnancies. These physicians need not have the skills for handling surgical intervention as long as they can provide appropriate referral services.

Labeling

The Label (package insert), Physician Agreement, Order Form, Patient Agreement and the Medication Guide are to be designed to educate the patient and physician regarding the mifepristone regimen. In addition, certain procedures and issues must be addressed that will reduce patient risk. These issues are:

The patients should have clear access to medical care should a surgical abortion be required or complication occur. The dispensing physician can provide these services or the patient can be referred to these services. However, in either case instruction should be given to the patient about what to do in the event of an emergency following administration of mifepristone.

The patient should return to the clinic on day 3 to receive misoprostol.

Division's Current Reviews Assessing Approvabilty of NDA 20-687

Chemistry/Manufacturing/Controls Review

In May 2000, the sponsor submitted new analytic, physical, and stability data, which were reviewed and found to be adequate to assure the quality of drug manufacturing. An inspection of the bulk drug substance maker was performed on July 24-28, 2000 in which deficiencies were cited. These were corrected and the corrections were found to be acceptable. The tradename, Mifeprex, is found to be acceptable.

Information in the appropriate sections of the label were found to be adequate

Pharmacology/Toxicology Review

Table 2, which describes on-going pregnancies after mifepristone treatment, not terminated by surgery, was updated. There are no additional cases of congenital malformations. There is insufficient evidence for the Agency to conclude that there is a causal relationship between use of mifepristone alone or in combination with a prostaglandin and fetal malformation. However, information that fetal malformation is a possible risk is included in the physician's and patient's educational material.

Information in the appropriate sections of the label were reviewed and found to be adequate.

Biopharmaceutics Review

The major focus during the current review cycle was the potential for drug interactions with and by mifepristone because CYP 3A4 is involved in its metabolism. Drugs are mentioned in the label that might inhibit or induce the metabolism of mifepristone.

In addition, coadministration of mifepristone may lead to an increase in serum levels of drugs that are substrates for CYP 3A4. Since mifepristone is slowly eliminated (half-life of 12 to 72 hours), an interaction could occur for a prolonged period of time after administration. This may become clinically important since some anesthetic drugs are metabolized by CYP 3A4 and a small proportion of mifepristone patients will require surgery and anesthesia.

The above, as well as other information in the appropriate sections of the label were reviewed and found to be adequate.

Clinical Review
The primary medical officer, who has reviewed the sponsor's application each time, again recommended approval of the application from a clinical standpoint. The medical officer reviewed the labeling and associated material and found them to be appropriate.

In addition, the medical officer reviewed Safety Update No. 3 and found that the "Safety
Update Report is consistent with the cumulative experience gained to date and does not reveal any unexpected, unanticipated safety issues that would change the benefit to risk ratio."

Assessment

The clinical, pharmacology/toxicology, biopharmaceutics, and chemistry reviews were assessed. All recommended approval as previous deficiencies were satisfactorily addressed.

The six phase 4 commitments (see **Background**) communicated to the sponsor in the September 1996 letter, will be addressed by a program that includes two post-marketing studies. The first is a cohort-based study on the safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. The second one is a surveillance study on outcomes of ongoing pregnancies. Study questions regarding age, smoking and day 14 follow-up will be incorporated into the cohort study as well an audit of signed Patient Agreement forms.

The Label (package insert), Physician Agreement and Order Form, Patient Agreement and Medication Guide were reviewed and found to satisfactorily address previous deficiencies.

Conclusion

An approval action is recommended for NDA 20-687.

/S/

9/14/00

DRUDP/CDER/FDA

APPEARS THIS WAY
ON ORIGINAL

PDR® entry for
Cytotec Tablets (Searle)

Warnings

CONTRAINDICATIONS AND WARNINGS

Cytotec (misoprostol) is contraindicated, because of its abortifacient property, in women who are pregnant. (See *Precautions* .) Patients must be advised of the abortifacient property and warned not to give the drug to others. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to misuse of misoprostol as an abortifacient have been received. Cytotec should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Cytotec may be prescribed if the patient

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin Cytotec only on the second or third day of the next normal menstrual period.

(*back to top*)

DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):

ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to prevent duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to prevent gastric ulcers in controlled studies of three months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

(*back to top*)

CONTRAINDICATIONS

See boxed *CONTRAINDICATIONS AND WARNINGS*.

Cytotec should not be taken by anyone with a history of allergy to prostaglandins.

(*back to top*)

WARNINGS

See boxed *CONTRAINDICATIONS AND WARNINGS*.

(*back to top*)

PRECAUTIONS

Information for patients: Cytotec is contraindicated in women who are pregnant, and should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of complications from gastric ulcers associated with the use of the NSAID, or is at high risk of developing gastric ulceration. Women of childbearing potential should be told that they must not be pregnant when Cytotec therapy is initiated, and that they must use an effective contraception method while taking Cytotec.

See boxed *CONTRAINDICATIONS AND WARNINGS*.

Patients should be advised of the following:

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician.

If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: Cytotec must not be used by pregnant women. Cytotec may cause miscarriage. Miscarriages caused by Cytotec may be incomplete, which could lead to potentially dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death.

Cytotec is available only as a unit-of-use package that includes a leaflet containing patient information. See *Patient Information* at the end of this labeling.

(*back to top*)

Drug interactions: See *Clinical Pharmacology*. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

Animal toxicology: A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to 1 year.

An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.

Carcinogenesis, mutagenesis, impairment of fertility: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

Pregnancy: Pregnancy Category X. See boxed *CONTRAINDICATIONS AND WARNINGS.*

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. Cytotec produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by Cytotec may be incomplete. In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%. Anecdotal reports, primarily from Brazil, of

Phase III trials, and a gp120 antigen/QS-21 combination is in *Phase II.*

Aquila's development program with Elan is investigating an Alzheimer's vaccine ("The Pink Sheet" July 17, p. 20). "*Phase I* studies in the U.S. have been completed and additional studies are underway in Europe using a multi-immunization schedule," Aquila CEO Alison Taunton-Rigby, PhD, said during the conference call.

Aquila also has two cancer vaccine programs with Progenics Pharmaceuticals and Bristol-Myers Squibb. Aventis Pasteur has licensed QS-21 for use in its HIV vaccine programs.

SmithKline licenses QS-21 for use in several vaccines. The company has completed *Phase II* trials in therapeutic vaccines for Human Papillomavirus and Hepatitis B. Pediatric clinical trials with a prophylactic malaria vaccine in Africa will begin this fall.

SmithKline also has a QS-21 vaccine for herpes in *Phase I.* Aquila indicated that SmithKline's merger with Glaxo Wellcome will not affect the licensing arrangement. The Federal Trade Commission will likely require SmithKline to divest the antiherpetic ***Famvir*** (famciclovir) to secure antitrust clearance for the planned merger ("The Pink Sheet" July 31, p. 17).

The FTC has also requested Glaxo forego its rights to a prophylactic vaccine for genital herpes under development with Cantab Pharmaceuticals. Glaxo will continue its license arrangement to develop a therapeutic form of the vaccine, Cantab indicated. The company intends to sign another development partner for the prophylactic version. SmithKline licenses a genital warts vaccine from Cantab, and that deal is expected to continue. ♦ ♦

Searle *Cytotec* Pregnancy Reminder Issued As RU-486 Action Nears

Searle issued a reminder Aug. 23 that its gastric ulcer treatment ***Cytotec*** (misoprostol) is contraindicated for use in pregnant women, about a month before FDA action is expected on the pending NDA for mifepristone.

The Population Council's oral abortifacient RU-486 calls for a regimen of 600 mg mifepristone (three 200 mg tablets) followed two days later by 400 mcg of misoprostol. The group expects FDA action on the mifepristone NDA by Sept. 30 ("The Pink Sheet" June 12, p. 14).

Searle sent its "important drug warning concerning unapproved use of intravaginal or oral misoprostol in pregnant women for induction of labor or abortion" to physicians Aug. 23.

The "Dear Health Care Provider" letter states that "Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion." Cytotec is indicated for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers.

Searle said it "has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy."

The letter was drafted in collaboration with FDA, the agency indicated. MedWatch data was used to

collect information regarding adverse event reports, FDA said.

"Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain," Searle's letter explains.

In the letter, Searle (now part of Pharmacia) distances itself from the connection between Cytotec and its potential use in combination with mifepristone, noting that although "the uterotonic effect of Cytotec is an inherent property" of the prostaglandin product, "Cytotec is not approved for the induction of labor or abortion."

"Searle promotes the use of Cytotec only for its approved indication," the letter states.

The letter also emphasizes that the company has not and does not plan to conduct trials of Cytotec as an aid to abortion.

Searle "has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses."

"Therefore, Searle is unable to provide complete risk information for Cytotec when it is used for such purposes."

The company's efforts to avoid the product's use in pregnant women could help to protect it from any negative publicity from anti-abortion groups that an approval of RU-486 could bring.

In France, where mifepristone has been available since 1989, the Ministry of Health directed Searle to change Cytotec labeling, which included a contraindication for use in pregnant women, to allow for its administration to pregnant women in specialized hospitals.

After a positive advisory committee review of mifepristone in July 1996, FDA said it planned to meet with Searle to discuss a possible labeling change.

FDA indicated that a Cytotec labeling change continues to be a possibility and will likely be discussed as part of the RU-486 review.

Searle's reminder to physicians, which emphasizes the "known and unknown acute risks to the mother and fetus" associated with misoprostol use, suggests the company may be opposed to changing the contraindication.

Mifepristone has been "approvable" since September 1996. The application has suffered delays due to difficulties retaining a manufacturer.

A second "approvable" letter issued in February addressed labeling, manufacturing/chemistry and distribution issues, the Population Council said. The nonprofit institution and its distribution/marketing partner Danco responded to the second "approvable" letter at the end of March. ♦ ♦

SEP 11 2000

Memorandum

To: NDA 20-687, Mifeprex (mifepristone) Tablets, 200 mg
Addendum to Chemistry Review #5.

Through: ——— /S/ 9/8/00

From: ——— /S/ 9/8/00

Date: September 8, 2000

Re: Reference standard specifications, ——— molecular weight calculation

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This addendum to Chemistry Review #5 is to clarify the specifications for the mifepristone reference standard [see January 28, 2000 (#040) and September 8, 2000 (#059) amendments] and the calculation of the theoretical molecular weight used in the ——— analysis. As stated in Amendment #040, the mifepristone reference standard is derived through additional ———of a released batch of bulk drug substance (see Chemistry Review #4). After ——— the drug substance is then tested according to the following attributes in order to qualify as a reference standard: 1) description, 2) assay, 3) ———, 3) specific rotation, 4) melting range, 5) related impurities, 6) water content and 7) residual ——— The current mifepristone reference standard is derived from bulk drug substance batch #990101. This batch was characterized by ———

———

The calculated molecular weight of mifepristone is 429.2670. This molecular weight is based on using the atomic weight of the ——— of each atom, rather than using the average atomic weight of each atom (as listed in Periodic table). Based on the average atomic weights, the molecular weight of mifepristone is 429.6024. Since the ——— determination of the atomic weight of a molecule is based on the analysis of the ——— ——— calculation based on isotope mass is more accurate. Therefore, this is consistent with the observed mass of 429.2651.

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580, ———
HFD-580/ ———

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 24 2000

FROM: _____
Division of Drug Risk Evaluation II, HFD-440

THROUGH: /S/
Division of Drug Risk Evaluation II, HFD-440

TO: _____
Division of Reproductive and Urologic Drug, HFD-580

SUBJECT: Addendum to August 2nd Consult on "Review of a Proposed Phase IV protocols for Mifepristone (RU 486)"

PID#: D000526 **NDA #:** 20-687

I. Introduction

The addendum is in response to review division's request on establishing a standard for a Phase IV study protocol, following our prior consult dated August 2nd 2000.

Mifepristone, an abortifacient, is currently under FDA review. While the drug was judged "approvable" in term of its safety and efficacy four year ago, questions or concerns remain with regard to effective and safe use of the drug once it is marketed in the United States. Those concerns include, but are not limited to, adequacy of the distribution system, long-term outcomes of multiple use of the treatment regime, compliance with the treatment protocol, and effectiveness and safety of the drug for special patient populations.

The sponsor agreed to conduct post-marketing studies to address the above concerns in 1996 and recently submitted a study proposal to reaffirm its commitment. However, the study protocol was judged as inadequate in our prior review. During an internal meeting with the review division, a request was made to develop a standard for an adequate Phase IV study protocol.

II. The basic elements for a Phase IV study protocol:

While no standard currently exists, it is reasonable to expect the following elements to be included in a Phase IV study protocol.

Section I: Scientific and Technical Components:

1. Introduction/background
2. Objectives
3. Study design, materials and methods
   A. Study approach: specifying type of the epidemiological study, i.e. cohort, case-control or cross sectional.
   B. Data source: specifying study sites or existing databases to be used (be sure to include some demographic information of the study sites and targeted patients of interest to demonstrate feasibility of the study)
   C. Inclusion and exclusion criteria
   D. Data collection methods
   E. Defining outcome variable
   F. Defining main independent and confounding variables
   G. Analytical plan: specifying study sample size estimate, power, and appropriate statistical methods to be used
   H. Strengths and limitations, including potential sources of biases and bias control strategies

Section II: Administrative Components:

1. CV of Principal Investigators
2. Milestones for study progress
3. Time schedule for progress reports and final report

/S/ 5/24/2000

Concur:

/S/ 5/24/00

APPEARS THIS WAY
ON ORIGINAL

Memorandum

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

Through: [redacted] /S/ 6/20/00

From: [redacted] /S/ 6/20/00

Date: June 20, 2000

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

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

APPEARS THIS WAY
ON ORIGINAL

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

Filename: [redacted]

FEB 16 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 16, 2000

FROM: [redacted] /S/ 2/16/00
Concur. /S/ 2/16/00
Office of Clinical Pharmacology and Biopharmaceutics

SUBJECT: NDA 20-687

TO: File

The dissolution method and specification have been addressed by the Clinical Pharmacology and Biopharmaceutics review team and has been addressed in the Chemistry Review #4. The information conveyed is as follows:

Dissolution method and Specifications
Apparatus: USP 2 (paddle)
Medium: 0.01 N Hydrochloric acid
Speed: 50 RPM
Volume: 900 ml
Temperature: 37°C
Specification: [redacted]

APPEARS THIS WAY
ON ORIGINAL

Memorandum

FEB 15 2000

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

Addendum to Chemistry Review #4.

Through: ——— /S/ 2/15/00

From: ——— 2/15/00

Date: February 15, 2000

Re: Establishment Evaluation Request

Following re-inspection of the ——— facility on February 11, 2000, the District issued an acceptable recommendation. **However, the overall recommendation by the Office of Compliance is withhold (see attached EER).**

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580 ———
HFD-580' ———

Filename: ———

APPEARS THIS WAY
ON ORIGINAL

FEB 14 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: [redacted] (HFD-715)

TO: NDA 20-687 (HFD-580)

SUBJECT: Statistical comments on Amendment 024

A statistical evaluation of the European studies was completed previously. The clinical results of the supporting U.S. studies that are in amendment 024 are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required.

/S/
2/14/00

cc:
Archival NDA 20-687
HFD-580
HFD-715/Division files

APPEARS THIS WAY
ON ORIGINAL

Memorandum

FEB 11 2000

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

From: ——— /S/ 2/11/00

Date: February 11, 2000

Re: T-con with ——— (Office of Compliance/Division of Prescription Drug Compliance and Surveillance

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I contacted —— to discuss whether the shipping cartons need to have the same full labeling as on the blister package and secondary carton. I described to him that the shipping configuration is as follows: unit dose blister packages are placed in secondary cardboard cartons, then 12 cartons are placed in an intermediate cardboard shipper and sealed with tamper-proof tape, and finally 8 intermediate shippers are placed in a cardboard shipping case and sealed with tamper-proof tape. The intermediate shippers and shipping cases are only labeled with the NDC number, shipper code or case code, expiration date, and bar code. ——— recommendation was that the labeling was adequate because the blister package and secondary package have the complete labeling information.

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580/ ——
HFD-580 ———

APPEARS THIS WAY
ON ORIGINAL

Filename: ———

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 2, 2000

TO: [redacted] Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: [redacted]
[redacted] HFD-45
Division of Scientific Investigations

FROM: [redacted]
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-687

APPLICANT: Population Council

DRUG: Mifepristone

THERAPEUTIC CLASSIFICATION: (1) Priority Review

INDICATION: Contraception

REVIEW DIVISION GOAL DATE: January 7, 2000
ACTION GOAL DATE (PDUFA Date): February 19, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this NDA submission is contraception.

APPEARS THIS WAY
ON ORIGINAL

II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Daniel Mishell, M.D.	Los Angeles, CA	10/1/99	2/1/00	NAI/00076
Suzanne Poppema, M.D.	Seattle, WA	10/1/99	12/28/99	NAI/09946
Susan Haskell, M.D.	Des Moines, IA	10/1/99	11/29/99	NAI/09917

Site #1
Susan Haskell, M.D.
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314
Acceptable

a. The field investigator reviewed 118 records from a total of 236.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

Site #2
Suzane T. Poppema, M.D.
Aurora Medical Services
1207 North Street, Suite 214
Seattle, WA 98133
Acceptable

a. The field investigator inspected portions of the study-related records for 65 of the 164 subjects enrolled in protocol #166 A at Dr. Poppema's site.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

Site #3
Daniel R. Mishell, Jr., M.D.
LAC/USC Medical Center
1240 North Mission Road
Room2K1
Los Angeles, CA 90033
Acceptable

a. The field investigator inspected the study-related records for 15 of the 204 subjects enrolled in protocol #166 A at Dr. Mishell's site.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, no violations were observed that would affect the reliability or integrity of the data submitted in support of this NDA.

Follow-up action: None needed

/S/ 2/2/05

DSI/GCPBI

CONCURRENCE:

/S/

Division of Scientific Investigations

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

COMPLIANCE REVIEW

DATE: February 2, 2000

TO: Administrative File Number 00076
FROM: [redacted]
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: NDA 20-687

REVIEW OF: Daniel R. Mishell, M.D.
1240 North Mission Road
Room 2k1
Los Angeles, CA 90033

INSPECTION DATES: December 9-14, 1999

DISTRICT OFFICE/FDA INVESTIGATOR: Los Angeles Office/ [redacted]

DISTRICT CLASSIFICATION: NAI

BACKGROUND:

This was a routine inspection in support of the NDA listed above. This is the fourth inspection of Dr. Mishell. He was previously inspected on February 1, 1979, for a study on IND [redacted] A VAI2 letter was issued for this study. Another inspection took place on May 8, 1989 for NDA 19-897. A VAI2 letter was issued for this study. Another inspection took place on May 30, 1996, for NDA 20-544. A VAI letter was issued for this study. All three of these studies were sponsored by The Population Council. Dr. Mishell has been or is currently involved in clinical studies for [redacted] INDs as listed in COMIS.

ANALYSIS OF INSPECTION FINDINGS:

This was a routine inspection accompanied by the usual supporting exhibits. No Form 483 was issued by the inspector. After review of the inspector's report, I concur with the inspector's findings. It should be noted that the inspector reviewed only 15 subject files of the 192 subjects completing the study; this is an unusually small percentage of the files available for review. There were no limitations on the inspection, EIR, and/or interpretation.

CONCLUSION AND RECOMMENDATION:

The letter was classified NAI as no regulatory concerns were identified. No additional regulatory follow-up is needed.

/S/ 2/2/00

[redacted]

Compliance Review – Daniel R. Mishell, M.D.

CONCURRENCE:

Concur: /S/ Date: 2/9/00

Nonconcur: _____ Date: _____
(See attached supervisory comments regarding non-concurrence)

_____
Division of Scientific Investigations

FINAL CLASSIFICATION: NAI

Distribution:
HFA-224
HFD-45/Reading File
DSI File Number 00076

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

TO: [redacted]
[redacted] Office of Drug Evaluation III

FROM: Susan Allen, MD, MPH /S/ 1/12/00
Team Leader, Division of Reproductive and Urologic Drug Products

DATE: January 12, 2000

SUBJECT: Notification of Commitment to Recuse

RECUSAL UNDER 5 C.F.R. § 2635.502.

I have the following relationship: Prior to accepting employment at the FDA, I was associated with an organization that was to be involved in the introduction of the drug product mifepristone in the United States. Since 1997, I have had no further involvement with this drug product. From the first day of my employment with the FDA, in accordance with 5 C.F.R. § 2635.502, I have recused myself from participation in all official matters related to this drug product as described below.

Although I no longer have a covered relationship within the meaning of 5 C.F.R. § 2635.502, based on guidance contained in 5 C.F.R. § 2635.502(a)(2), I have elected to continue my recusal of the product mifepristone. In my position of [redacted] in the Division of Reproductive and Urologic Drug Products, Office of Review Management, Center for Drug Evaluation and Research of the Food and Drug Administration, I may be called upon to participate in certain particular matters involving specific parties that could affect the NDA review process for mifepristone. These matters may include the following:

- Participating in internal meetings, teleconferences and/or industry meetings related to the NDA review process for mifepristone;
- Review of and response to written or verbal inquiries from the current NDA sponsor or any of its current or future licensees regarding the NDA review process for mifepristone;
- Responding to internal inquiries from other divisions or offices within the FDA related either to mifepristone or to progress on the review of the NDA for this drug product;
- Responding to inquiries from individuals or parties external to the FDA regarding mifepristone or the NDA review process for this drug product.