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To: Heather H. Howard/OPD/EOP

cc:
Subject: Mifepristone overseas

I heard you might need help with mifepristone's use overseas. I can help. Let me know if this document doesn't get you what you need, and I'll connect you to more.

Mifepristone in Europe - June 2000

Current status in Europe

C Mifepristone is registered in the following European countries: France (1988), United Kingdom (1991), Sweden (1992), Austria, Belgium, Denmark, Finland, Germany, Greece, Netherlands, Norway, Spain, Switzerland (July 1999), as well as Israel (1999).

C In the 13 European countries (and Israel) where mifepristone has been approved, national laws govern abortion provision. Various levels of hospitals, clinics, and authorized centers may provide the service, depending on the country. The mifepristone regimen has fallen under the existing abortion laws, designed for surgical abortion. Generally, abortions are provided free, or at low cost, in these countries.

France
C The country with the widest experience is France.

C All abortions are performed in some 800 government authorized public or private hospital centers under French abortion law.

C Mifepristone may be used up to 49 days from the last menstrual period. The drug combination (mifepristone and misoprostol) is the same as that proposed for the United States.

C Legal requirements include a week's compulsory reflection between the first medical consultation and the abortion; this delays administration of mifepristone and results in some patients becoming ineligible for the procedure.

C Three visits are required: Day 1: mifepristone tablets are swallowed in the presence of a doctor or nurse; Day 3: misoprostol is taken orally; the woman stays at the hospital clinic for three hours under observation; Days 10-14: follow-up visit.

C There is no official protocol for the use of ultrasound and most procedures are performed without its use.

C In 1998, one-third of the 180,000 abortions in France were medical abortions.

Sweden

C Although medical abortion has been available since 1992, it is not been widely used until recently. In 1998, 35 percent of abortions performed in the first trimester were medical abortions.

C The regimen can be used up to 63 days since the last menstrual period. Mifepristone taken orally is followed two days later by gemeprost taken vaginally.

C Under Swedish abortion law, abortions are provided in hospital clinics.

United Kingdom

C The National Health Service (NHS) pays for three-quarters of all abortions in England and Wales and carries out almost all abortions in Scotland.

C In England and Wales in 1998, almost half of the abortions were provided within NHS hospitals and 25 percent were provided by independent nonprofit organizations and paid for by NHS, while 26 percent were provided by the same nonprofit organizations but were paid for by the women.

C Abortions are provided in government hospitals, private hospitals, and clinics.

C In 1998, 7 percent of 190,000 abortions performed were medical abortions.

C The regimen is used up to 63 days since the last menstrual period. Under the licensed regimen, 600mg of oral mifepristone is followed 33 to 48 hours later by 1g of vaginal gemeprost. The woman remains in the hospital for six hours. An alternative regimen followed by many clinics uses 200mg of oral mifepristone and 800mcg of vaginal misoprostol.

C As seen from the alternative regimen described above, NHS providers are able to be more flexible with regimens because restrictions are not placed on NHS delivery provided it is within the law. In 1997, the Royal College of Obstetricians and Gynecologists listed among recommendations related to medical abortion that 200 mg is an adequate dose.

Facts relevant to mifepristone provision in the United States

C In the 10 years since mifepristone medical abortions have been provided, there has been much experience in the provision of the mifepristone-misoprostol regimen.

C Studies conducted in the United States and elsewhere since 1996 have demonstrated that it is safe and feasible to vary the way the method is provided from the original French regimen, for example, by permitting home use of the second drug (misoprostol) and reducing the mifepristone dose from 600 mg to 200 mg.

C Experience with methotrexate, another drug used for early medical abortion, also has demonstrated the safety and efficacy of home use of misoprostol.

C Abortions in the United States are provided by a range of physicians-including obstetrician/gynecologists and family physicians. There are no laws in the United States that restrict performance of abortions to specific categories of physicians, and it is legal for abortions to be performed in private doctors' offices as well as in clinics.

C Any drug's labeling reflects both the legal situation in the country and the wishes of the company marketing the product. The labeling proposed by the original French company more than a decade ago is very conservative and restrictive. This has resulted in many of these original restrictions being included in recent country approvals.

References

Medical Abortion: Meeting Women's Needs, report of a seminar on 14 October 1999, UK FPA and the Population Council, 2000.

Medical Abortion, Journal of the American Medical Women's Association, Vol. 55, No. 3, Supplement 2000.

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From:

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MESSAGE:

Notes on the use of Mifepristone. Please keep confidential.

MEDICAL ABORTION IN THE U.S.: CURRENT AND FUTURE PROSPECTS

The Population Council, NY NY
June 2, 2000

Registration and Public Information

U.S.

Roy Karnovsky, of Danco: Just yesterday (6/1) heard from FDA, will have to address several more issues/obstacles before mifepristone is approved. *Was* hoping for final approval by September 2000. (Process began in 1996.) Home administration/use is going to be an issue. Rumor has it that the FDA will do a "conservative" read of labeling instructions. Provider "entitlement" (FDA language) will be an issue, may require them to be registered physicians, located within certain distance from a medical facility (←how to measure this? Time or distance? During which time of day, which method of transport, etc.) Danco will need to respond to these issues in the next few weeks (KM memo says 3rd week of June.)

Richard Hausknecht: Thalomide is the only other non-narcotic drug in US subjected to these types of restrictions (e.g., issues of "entitlement"). Originally they tried to do the same thing (place restrictions) with Depo.

There are no FDA restrictions on methotrexate because it is used off-label.

Karnovsky: Not sure that the FDA maneuvering is politically (e.g., conservatively) motivated, they're probably just being cautious. (In response to whether we need to rally political support for approval) At first it could have hurt, but that probably would not be the situation now.

Trussel: Considering the circumstances, the FDA has actually been generous so far.

The patent on misoprostol expires in July 2000.

It was decided during this part of the meeting that interested participants can convene during the second half of lunch to discuss political strategies for gaining approval of mifepristone.

Canada

Ellen Wiebe: On April 26, 2000 received permission/approval from Health Canada (= FDA) to conduct mifepristone trials. Has been doing trials with methotrexate for several years. Had trouble getting a drug company to supply because of safety concerns, they wanted the U.S. to approve mifepristone first. Also had to do the application herself because companies that normally provide these services were unwilling to do so in this instance. Should start study in July.

Europe

In all but France and Scandinavian countries government authorities are afraid of the issue, don't want to deal with it. Example of Austrian and German governments, which chose anti-choice folks to oversee approval process and ended up originally restricting administration of abortion drugs to 3-4 day window (days 46-49). Doctors were not reimbursed for performing this procedure. Other countries restrict administration to hospitals, even though relatively few abortions provided at these facilities. Some countries are conducting trials using prostaglandin other than misoprostol.

homeuse Home use (of miso) is an issue in Europe. Home administration is a unique American (US and Canada) experience. (Later on, however, we learn that some developing countries allow for home administration, at least in cases medical abortion where misoprostol alone is used.)

In UK, where mifepristone was approved in 1991, there is a lot of regional variation in access and availability. Overall, 1/3 of abortions are medical, but in some regions as high as 75%. Getting ready to distribute booklet about abortion (medical only?) to 14-16 years olds in school! (Unfortunately, there were not enough copies and I was unable to get one.)

In France, the government recommends 600 mg of mifepristone and it is distributed in this dosage, but many doctors only use 200 mg. Based on distribution, 1/3 of all abortions are medical, 50% of early abortions, but we know these %s are actually higher. One provider at the meeting noted that 90+% of the early abortions at her clinic are medical, even though she offers both medical and surgical option.

Searle, makers of Cytotec (misoprostol), urged some European government officials to specify on label that misoprostol should not be used as an abortifacient.

Developing Countries
Mifepristone has been available in China for a "long time" and is widely used. Will be approved in South Africa shortly. Is approved in Israel and Russia, though not easy to access in the latter.

Public Education
Based on focus group research, Danco will be referring to "termination or pregnancy" and "early option" as opposed to medical abortion or abortion pill (an anti-choice term). Soon to come, the earlyoptionpill.com website.

Danco will have a huge media push when approval received, tentatively slated for Sept. 30, 2000

All meeting participants received a recently published issue of JAMWA, devoted entirely to the issue of medical abortion. It is JAMWA's hope that this will serve as the "bible" of medical abortion. The issue can be accessed online.

Updates and Current Research
(NOTE: This portion of the meeting included detailed discussions of dosages and methods of administration that I was sometimes unable to follow.)

Eric Shaff (U of Rochester): publishing findings from study showing that using mifepristone up to 9 wks does not reduce efficacy. There is some flexibility in Misoprostol administrations and it appears that it can be administered within 24-72 hours of mifepristone. Forthcoming research will determine if ultrasounds are necessary. Trying to research medical abortions among minors, but having a hard time recruiting participants. Burnhill study found the mifepristone worked better in minors.

Carolyn Westoff: features they are exploring in research include (see abstracts)
personnel time - medical abortions are cheaper
quality of life issues - surgical abortion patients initially less satisfied but ultimately found no difference between medical and surgical abortion
pain medication - more likely to use during home administration but appears to be determined by provider(?)
medical abortion failures – in clinical trials involving 4,393 women resulted in 117 (2.7%) failures, defined as surgical interventions. More common among women who had previous abortions. Reasons for surgical intervention include excessive bleeding (52%), continuing pregnancy (15%) and other reasons (33%).

It is not known if Mifepristone can be used to treat ectopic pregnancies, but trials are being set up.

Ellen Wiebe: Studied time loss from work. Notably, she did not control for lots of variables, but she found that surgical abortion patients took more time off from work as did medical abortion patients. (In US, both groups took off same amount of time.)

Trussel, Garcia, and ???? are going to do a meta-analysis of medical abortion studies, int'l in scope (Kahn et al recently published a meta-analysis on medical abortion)

Ann Gerhardt, Stan, and Carol Joffe intend to study medical abortion outside of NAF providers.

John Jain (LAC & VSC Medical Center): (I think this was him) Has used misoprostol alone for medical abortions. 2 doses are required instead of 1. 75% of women abort at first dose. In India (and Vietnam, I think) misoprostol alone is used for abortions. Even though efficacy rates is only 50-60% AND women are informed of this, over 90% choose this method over methotrexate because misoprostol is administered at home. (this information created quite a stir.)

Richard Hausknecht (Danco, Sinai): Recognize that US government will never approve use of misoprostol alone for medical abortion.

Other uses for misoprostol: missed/incomplete abortion, early fetal death

Issues not addressed in research yet: long-term effects of mifepristone, effects of multiple medical abortions, liability for incomplete medical abortions, esp. if there are birth defects (some of these were actually brought up later in meeting).

(Break for lunch. I was not able to sit in on the strategy session.)

Service and Delivery

Mid-level providers

A potential new strategy: During medical abortion the woman's body provides the abortion (as opposed to another person). Current abortion laws and restrictions apply to surgery, so they may not apply to mid-levels.

Bonnie Scott Jones (CRLP): Well, not really...(first, recognize that while some laws are intended to restrict access to abortion, some of them are necessary to insure safety.)

Distribution system

Roy Karnovsky: Danco submitted a detailed plan for distributing mifepristone. (1) providers will have to be registered physicians and distributions will have a serial # so they can be tracked (2) providers have to give detailed information to patients regarding the procedure, drug actions, side effects, efficacy, etc. They felt that this was a necessarily restrictive plan. HOWEVER...

The FDA did not. Current requirements suggested by FDA include provider has to perform surgical abortions, provider has to use ultrasound, have training in mifepristone, and have admitting privileges. Something about issues of third party qualifications (I'm not sure what this term means). Again, Danco has to come up with convincing arguments as to why these criteria are not needed in order for them not to be implemented.

Trussel: not necessarily politically motivated. Don't underestimate the power of stupidity when it comes to government bureaucracy.

Phase IV and post-marketing surveillance

PPFA is monitoring prevalence of medical abortion in their own facilities, NAF keeps stats on members. Danco will have an idea of prevalence based on serial number monitoring and will also keep track of complications.

At this point I was asked to explain how AGI monitors or intends to monitor, medical abortion. I summarized the administration of the provider survey, the sampling of ob/gyns. Trussel had to clarify that our unit of analysis is abortions, not doses.

Shelly Clark (Pop Coucil, works with Danco a lot): Expressed some ambivalence about the need and accuracy for statistics on prevalence and # of abortions, but acknowledged that it was probably necessary in order to monitor (lack of increase in) # of abortions once mifepristone is approved.

In France, the number of abortions did not increase with the introduction of medical abortion.

Future Issues

Is ultrasound necessary? There are studies showing that in most cases, women can provide a relatively accurate estimate their gestational age (compared to ultrasound).

Burnhill: Sue Haskell (NAF poster session) found that a substantial % of doctors (and women?) incorrectly estimate gestational age (based on LMP, not ultrasound)

PPFA will require ultrasound in cases of medical abortion.

Be prepared for adverse events (e.g., women who do not keep their follow-up appointments)

What will happen when the patent for misoprostol expires? Several generic drug companies are applying. Currently, there are 40-60 pills per bottle and hopefully more convenient packaging will appear (so more convenient for purchase by those who provide relatively few abortions.)

The more uses of mifepristone, the better. Currently, these include: brain tumors, fibroids, breast/cancer research (but findings are not promising here), inducing labor, emergency contraception.

Notably, EC folks not like idea of mifepristone being used for this purpose since it would taint their argument that EC is not abortion.

Notes from self (or, a few comments from RKJ)
The impact that medical abortion will have on abortion in general was never addressed. I think the assumption shared by many in attendance was that many women will opt for medical abortion and so the impact will be substantial. For example, when the issue of patient satisfaction came up, most, if not all, of the stats emphasized how much more convenient and desirable medical abortion was compared to surgical abortion. Little time was spent on issues such as the increased cost, bleeding, and "discomfort" associated with medical abortions. There was no discussion of patient characteristics and/or self-selection into the trials.

Early in the meeting Lindy Wood, of the Feminist Women's Health Center in Atlanta (which provides training for medical abortions), pointed out that some providers are not only unenthusiastic, but somewhat antagonistic, towards medical abortion. They don't like the idea of current non-providers encroaching on their territory. No one pursued this topic in discussion.

(Meeting attended by Rachel K. Jones)