Administration of mifepristone, 36 to 48 hours prior to prostaglandin induction of termination of pregnancy between 13 and 20 weeks gestation, significantly shortens the interval between the beginning of treatment with prostaglandin and foetal expulsion and reduces the dose of prostaglandin necessary for expulsion.

oduct licence number
rL 16152/0001

Date of issue
September 1997

Product licence holder: EXELGYN
6, rue Christophe Colomb
75008 Paris - FRANCE

M I F E G Y N E

Oct. 28, 1994

ROUSSEL

Sweden

Tablets 200 mg

Synthetic steroid with antiprogestational activity for termination of pregnancy ATC G03X B01

Declaration: 1 tablet contains: Mifepristone 200 mg, constit. q.s.

Properties: MIFEGYNE tablets contain as active substance mifepristone a synthetic steroid with anti-progestational action. Mifepristone inhibits through a competitive receptor interaction the effect of progesterone on the endometrium and the myometrium, which cause a dilatation and softening of cervix, and expulsion of the ovum. During pregnancy mifepristone increases the sensitivity of the myometrium to the contraction induced effect of prostaglandin. Mifepristone inhibits also the effect of glucocorticoids through a competitive receptor interaction.

Mifepristone in combination with a synthetic prostaglandin analogue, has a success rate of about 95% for termination of pregnancies of up to 9 weeks (63 days) of amenorrhoea. About 55% of the women start to bleed within 48 hours following the intake of mifepristone and about 96% within 4 hours following the administration of the prostaglandin. For termination of pregnancy in the second trimester some women start to bleed following the intake of mifepristone. About 1-2 hours following the administration of the prostaglandin, the abortion usually commence with a bleeding. It should be observed that the blood loss increase with the gestation time. The cycle following Mifepristone intake is ovulatory.

Pharmakokinetics: Following oral administration of a single 600 mg dose, the peak plasma level (about 2 mg/l) is obtained after about 1 h 30 minutes. The absolute bioavailability is 69% following an oral dose of 20 mg. Changed bioavailability following administration together with food has not been specially investigated. Mifepristone and at least one metabolite are in plasma bound to α_1- glycoprotein. The binding is sauterable which gives a non-linear kinetics. Three metabolites are formed which activity have not been studied in human. Following the distribution phase, elimination is slow at first with the plasma concentration decreasing by 50% between 12 and 72 hours, and then more rapidly giving an elimination half-life of about 18 hours. During 10 days a total amount of 9% of the given dose is excreted in the urine and 83% in the faeces.

Indications: Medical alternative to surgical termination of intrauterine pregnancy during the first trimester (up to 9 weeks /63 days amenorrhoea) based on the first day of the last menstrual period and/or ultrasound.
For use in combination with gemeprost for termination of pregnancy in the second trimester.

The product can only be prescribed by doctors whom according to the abortion law have the right to perform abortions. The product may from the pharmacy only be given out to the clinics where these doctors work. The product may not be given out to an individual patient following prescription on a recipe. During the abortion the general advices regarding use of the abortion law from the National Board of Health and Welfare (SOS FS 1989:6) should be regarded.

Contra-indications: Suspected ectopic pregnancy. Chronic adrenal failure. Long-term corticosteroid theraphy. Known allergy to mifepristone. Haemorrhagic disorders and treatment with anti-coagulants.

Precautions: Moderate or heavy smokers over 35 years when used in association with gemeprost. Renal or hepatic failure. All the precautions for administration of prostaglandin analogues must be observed. Special consideration must be given to patients in the following high risk catagories: asthmatics and other patients with COAD, patients with cardiovascular disease, experience of Caesarean section.

Pregnancy: B:3 Clinical experience from women continuing their pregnancy is limited. In animal studies teratogenic effects (brain injuries) have been documented in rabbits following doses giving plasmaconcentrations below therapeutic level. The patients should be well informed of this before starting the treatment.

Side effects: The most common side effect is abdominal pain which is experienced of 5-40%.

Frequent (>1/100)	Body as a whole:	Asthenia, weakness, malaise
	GI:	Abdominal pain, nausea, vomiting
Less Frequent	Skin:	Rash
	Other:	Bleeding leading to need for blood transfusion or curetage.

Side effects induced by the prostaglandin administration, see gemeprost.
An analgeticum can be prescribed to alleviate the abdominal pains, but see Interactions.

Dosage: First trimester abortion: 600 mg MIFEGYNE (3x200 mg) in a single dose in the presence of the doctor, see Observe.

The patient must return 36 to 48 hours later and unless abortion has already been completed, a 1 mg gemeprost pessary must be administered, see Observe. In the majority of cases abortion will occur within 4 hours following the administration of the prostaglandin.

A follow-up visit must always take place within a period of 8 to 14 days after administration of MIFEGYNE to verify by the appropriate means (clinical examination, ultrasound, ßHCG measurement etc) that the abortion is complete and that the vaginal bleeding has stopped or substantially reduced.

Second trimester abortion: 600 mg MIFEGYNE (3 x 200 mg) in a single dose, in the presence of the doctor, 36-48 hours prior to scheduled prostaglandin termination of pregnancy.

Interactions: Interaction studies have not been performed but NSAIDS and acetylsalicylic acid can theoretically modulate or inhibit prostaglandin synthesis and metabolism and should therefore be avoided.

Observe: The treatment procedure must be carefully explained to and completely understood by the patient before the administration of MIFEGYNE.

In the event of failure ot the method, the pregnancy must be terminated by another appropriate method.

The use of MIFEGYNE requires as other methods of abortion the prevention of rhesus immunisation.

The bleeding usually stops within 12 days but can continue during 3 weeks.

For first trimester abortion the following is also valid:
As there is a risk of hypotension following the prostaglandin administration it is recommended that the patient stays for observation during 4 to 6 ½ hours, or until the bleeding and/or pain have diminished. If the abortion has not occurred before the patient leaves the hospital, she must be informed whom she should contact in the event of any problem and particulary if a very heavy vaginal bleeding occurs.

The patient must be informed that the vaginal bleeding is in itself not in any way a proof of a complete abortion and a follow-up visit is therefore absolutely necessary.

The blood loss is usually considered as acceptable, in that it does not cause anemia.

Other: A patient information leaflet is provided by Roussel Nordiska AB to clinics concerned.

Packages and prices: Tablets 200 mg (biconvex, cylindrical, light yellow, 11 mm in diameter, with an identification code engraved on one face, and the Roussel logo on the opposite face).
3 s (blister pack)

The Population Council

Center for
Biomedical Research

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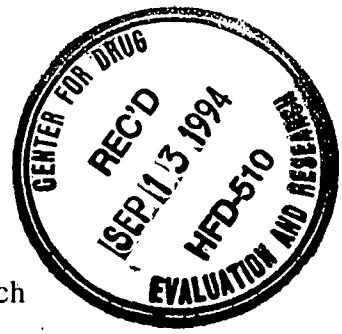
II/IM
ORIGINAL

September 8, 1994



noted -
9/18/94
ISI

Director, Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room, 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 103
Information Amendment: Pharmacology/Toxicology/Clinical

Dear ———

Noted
6 June 95

We refer to our above Investigational New Drug Application (IND) and also to our meeting with you on July 7, 1994 to discuss plans for initiation of clinical studies with mifepristone in inducing abortion.

As discussed in that meeting, to support our proposed studies with mifepristone, we wish to incorporate into this IND the portfolio of information provided earlier by Roussel Uclaf to the Food and Drug Administration and to The Population Council. Our amendment of August 3, 1994 (Submission Serial Number 100) included the chemistry, manufacturing and controls information provided by Roussel and this submission includes the preclinical and clinical information in the portfolio. The information has been reorganized into a format more typical of an IND submission.

Please advise me of any questions or comments regarding this submission.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin, M.D.
Director

Attachment