Supplementary embryotoxicity study in rats

This study was performed to test for teratogenicity at a clearly embryolethal dose. RU486 was administered by gavage to groups of 25 pregnant Sprague-Dawley rats from days 6 to 17 at a daily dose of 0 or 2 mg/kg.

Gestation was totally interrupted in 12/19 pregnant dams. Total post-implantation loss was 81% vs 10.5% in controls..

There was no difference in mean body wt in surviving fetuses between treated (49 survived) and controls (280 survived).

No malformations were seen in the treated group. There were no skeletal anomalies attributable to treatment (Table 3).

Exploratory study of the possible teratogenic or embryotoxic effects of RU 486 on the rat embryo in culture.

Embryos of Sprague-Dawley rats were taken from females sacrificed on day 10 post-mating. Embryos at the same stage of development were selected and groups of 12 embryos were cultured in rat serum with 0, 10 or 50 ug/ml RU486 for 1 or 3 hrs. Rotating 25 ml culture flasks each received 2 ml of culture medium with air gases and kept at a ph of 7.4 at 37 C. After the period of exposure to the drug, the embryo's were removed, rinsed and replaced in fresh culture medium and cultured for an additional period up to 48 hrs. After this time, the embryo's were examined for morphological anomalies and the diameter of the yolk sac was measured to evaluate growth. Only those embryo's alive at the end of the procedure were examined.

There was no effect of the drug on embryo survival. There was a significant dose-dependent inhibitory effect on the mean diameter of the yolk sac. There were 3 malformed embryo's, all in the 10 ug/ml for 3 hr group.

Embryotoxicity study in the rabbit.

Groups of 15 HY rabbits were gavaged with vehicle, 0.25, 0.50 or 1.0 mkd RU-486 from day 6 to day 18 of gestation. Rabbits were sacrificed on day 28, the day before parturition.

Mortality: 2 MD and 1 HD rabbit died during the study. Signs of pulmonary disease were noted. One LD rabbit was the victim of an intubation error and was eliminated from the study.

Body wt: day 28. Some dose-related decrease in wt gain. C-4445; LD-4325; MD-4260; HD-4247.

Mean number of fetuses per litter and their mean weight did not differ between control and treated groups.

There was 1 exencephaly in the controls; 1 in the LD and 1 acephaly in the MD. All fetuses in the HD were normal. There was interventricular communication in the heart in 2 LD and 1 MD fetus with none in the HD (Table 4).

Supplementary embryotoxicity study in rabbits.

This study was initiated to examine the effects of higher doses of RU-486 on embryotoxicity in rabbits.

20 HY rabbits (30 in the control group) were gavaged with 0, 2 or 4 mkd RU-486 from day 6 to day 18 of gestation. Sacrifice was on day 28.

Clinical signs: No treatment-related effects.

Body weights: On day 28; C-4124; LD-4062; HD-4158. No treatment related effects despite the significant fetal loss in the treated dams.

Embryolethality: 12/19 dams in the HD and 3/19 in the MD exhibited fetal loss. Fetal loss rates were 6%, 31% and 67% in C, MD and HD, respectively.

Mean number of viable fetuses was reduced. C- 8.89; MD-6.89; HD-2.84.

Fetal exam: One MD fetus (of 131) had exencephaly combined with palpebral (eye) opening, coelosomy, and torsion/flexion of a hind paw. Another MD fetus had cleft palate. One HD fetus (of 54) had generalized edema. There were various ossification defects in the controls and treated animals, involving the cranium, sternum or paws. The incidence was, in some cases, significantly higher in the treated animals than controls (Table 5).

New data on the hormonal requirement of the pregnant rabbit: "partial pregnancies" and fetal anomalies resulting from treatment with a hormonal antagonist given at a sub-abortive dose **A. Jost** C.R. Acad Sc.Paris t.303 Serie III, No 7, 1986.

This was a published report on the effects of RU486 in pregnant rabbits.

Forty pregnant Fauve de Bourgogne rabbits were injected with 250, 500, 750 ug or 1 mg RU486/dam for 1, 2, 3 or 5 days starting on day 11 of pregnancy. The doses are roughly equivalent to 0.08 - 0.33 mg/kg/day. The fetuses were removed on day 28. There were 22 abortions, 11 "partial pregnancies" and 7 had a number of fetuses that developed normally.

In the partial pregnancy or normal pregnancy groups, three dams in the 500 ug dose group and one in the 1 mg dose group had fetuses with malformations (failure of the cranium to close and hemorrhagic destruction of the upper part of the head and brain, no spinal column, no closure of the eyelids). There were no controls in this study; the author used data from a another study using 30 untreated pregnant rabbits of the same strain examined on day 20 and 47 rabbits examined on day 30. There were no anomalies in those groups.

These results from the studies by Roussel and the published report indicate that RU486 treatment may result in fetal malformations in rabbits. This effect is most likely due to a uterine effect resulting from progesterone withdrawal.

Peri- and postnatal study in the rat.

Because a normal fertility study could not be performed with RU486, the sponsor did an extensive peri- and postnatal study in rats with an examination of drug effects on the reproduction of the F_1 generation..

Groups of 20 (25 in C and HD) Sprague-Dawley rats were gavaged with 0, 0.25, 0.50 or 1 mkd RU-486 from day 15 of gestation to day 21 postpartum. Dams were allowed to litter naturally and pups were followed until offspring of the F_1 generation were born.

Body wt. The HD gp had a decreased mean bw gain during the last 5 days of treatment due to abortions.

Abortions: 2/19 in the MD and 8/21 in the HD. A preliminary study showed that a 2 mg/kg dose resulted in abortions in 5/7 dams.

The mean number of pups at birth was normal in all groups. The mortality rate at birth was 1.2% in controls and 4.1% in the HD animals but the difference was not statistically significant.

Examination of the F_1 offspring

The sex ratio was within normal limits, the vital index on days 4 and 21 was between 93-99% in all groups. At birth the mean weight was essentially the same in all groups. No malformations were seen even in the pups that died. End points of well being such as detachment of the pinna, eruption of teeth, growth of fur and eye opening were not affected by treatment.

In a test of neuromuscular development (righting reflex), 74% of controls responded adequately on day 6. In the treated rats the success rates were 66, 71 and 58% for LD, MD, and HD, respectively. The response in the HD was statistically significant ($p<0.01$).

In the rotarod test, a test of locomotor development, the proportion of young responding actively and the mean balancing time were slightly lower in the treated groups than in the control group

but the differences were not statistically significant.

In the water maze test (a study of behavior), the mean duration of an error-free test in males born to LD dams was 13.9 sec vs 10.2 sec in the controls (an improvement). The number of active young among females born to MD dams was 32% vs 71% in controls ($p<0.01$).

Sexual development

In female pups, vaginal opening was essentially the same between groups. In males, descent of testes was not affected by treatment.

Test of reproductive function

For F_1 males the rate of copulation was normal and for females, all mated females were pregnant and their pregnancy proceeded normally. All animals littered on the normal date, the mean number of pups was within normal limits for all groups and the mothers cared for their offspring and suckled them as appropriate.

Examination of F_2 offspring

The sex ratio was the same for all groups, the survival index on days 4 and 7 was 100% and the weights were equal and macroscopic exam did not reveal any treatment related lesions.

Combination of RU 38 486 and progesterone outcome of gestation in rats.

Five groups of 8 pregnant Sprague-Dawley rats were treated from day 6 to 12 of pregnancy. One group received only vehicle, two groups received progesterone only (50 and 100 mkd) and two groups received 2 mkd RU486 plus 50 or 100 mkd progesterone.

In the 50 mkd progesterone alone group the pregnancy rate was only 50% and the cause for this low rate is unknown. In the 100 mkd group the pregnancy rate was 100%. In the RU486 + 50 mkd progesterone the rate was 87% and in the RU486 + 100 mkd progesterone group the rate was 100%.

Fetal losses were 4.11 % and 10.78% in the RU486 gps getting 50 and 100 mkd progesterone respectively. The control rate was 2.70%.

Fetuses were examined externally only. There were no obvious malformations and the mean fetal weight was the same between treated and controls.

Combination of RU 38 486 and progesterone outcome of gestation in rabbits

This was a combination of two studies in HY rabbits. Groups of 10 females were given 4 or 8 mg/kg RU486 on day 6 or 7 to day 15 of gestation. Other groups received 100 mg/kg progesterone alone or RU + progesterone.

RU486 treatment alone resulted in 66% - 100% fetal loss. There was one abnormality (celosomia) in a HD fetus. In combination with progesterone, RU486 had no effect on gestation other than a slight reduction in fetal weight in the 4 + 100 mg/kg dose group.

Thus the abortifacient activity of RU486 is antagonized by progesterone allowing for normal pregnancy and delivery.

GENETIC TOXICOLOGY

Mutagenicity study using a bacteriological method Ames test with and without metabolic activation.

RU486 in DMSO was tested in a concentration range of 100 to 10,000 ug per plate using tester strains of S. typhimurium (TA 1535, TA 1537, TA 98 and TA 100) in the presence and absence of a S-9 mix metabolic activation system composed of hepatic microsomes obtained from -induced rat liver with the addition of cofactors.

No dose-related increase was seen in the number of spontaneous mutants per plate in two separate tests. Four different positive controls (different for different strains/activation system) were clearly positive.

The test was negative.

Gene conversion test in S. cerevisiae D4.

This test assessed the ability of RU486 to induce gene conversion on chromosomes of Saccharomyces cerevisiae yeast cells. RU486 in DMSO at concentrations of 10 to 125 ug/ml (precipitation occurred at the top dose) was added to plates of S. cerevisiae (D4 strain) prior to incubation in either adenine or tryptophan deficient media.

No significant differences were seem between the negative control and the RU486 treated plates with or without metabolic activation. The positive control did significantly increase the mutagen frequency.

The test was negative.

Forward mutation test in S. pombe P1.

RU486 in DMSO at concentrations of 10 to 125 ug/ml (precipitation occurred at the top dose) was added to suspensions of Schizosaccharomyces pombe yeast cells to determine the potential to induce forward mutations.

There was no increase in mutagenic frequency with RU486 with or without metabolic activation. The positive control produced a significant increase in mutants.

The test was negative.

Unscheduled DNA synthesis in cultured HeLa cells

RU486 was prepared in DMSO at concentrations of 1 to 100 ug/ml precipitation occurred at the top dose).

The repair of possible mutations produced by RU486 in human HeLa cells was evaluated by adding tritiated thymidine to the culture medium and assaying it at the end of the test by a The results show that RU486 did not include a significant increase in incorporation of tritiated thymidine in cultured human HeLa cells either in the presence or absence of metabolic activation. The positive control did significantly increase thymidine incorporation.

The test was negative.

In vitro chromosome analysis in CHO chinese hamster cells.

RU486 was studied at concentration of 20, 30 and 40 uM with and without metabolic activation. The exposure time was 4 hrs. There were no effects of the treatment on number of chromosome aberrations, including gaps in cultured Chinese hamster ovary cells. There was an increase with the positive control.

The test was negative.

In vitro gene mutation test in V79 chinese hamster cells.

RU486 was tested at concentrations of 5 to 45 uM with and without metabolic activation. No

mutagenic activity in V79 Chinese hamster lung cells was detected. The positive control did produce a significant increase in mutation frequency.

The test was negative.

Test for mutagenic activity micronucleus test in the mouse

RU486 was administered orally in a single dose of 1000 mg/kg dissolved in 0.25% carboxymethylcellulose. Fifty Swiss mice (males and females) per group were sacrificed 24, 48 or 72 hrs after treatment. The incidence of micronucleated cells was determined from a total of 2000 polychromatic erythrocytes per animal.

There was a decrease in the ratio of polychromatic to normochromatic erythrocytes in the group receiving RU486 at 48 hrs compared to the negative control (also seen in the positive controls at 48 and 72 hrs), indicating that the MTD had been reached. There was no increase in the frequency of micronucleated polychromatic erythrocytes at any time point. The positive controls of triethylenemelamine and dimethylbenzanthracene did produce increases in the mutation frequency.

The test was negative.

EVALUATION

Mifepristone has been tested in a variety of animal and in vitro systems and exhibits significant antiprogesterone, antiglucocorticoid activity with some antiandrogen activity.

Mifepristone exhibits little acute toxicity and the repeat dose toxicity is primarily what would be expected for a progesterone/glucocorticoid antagonist. Certain findings such as kidney toxicity in rats and monkeys that occurred in the six month repeat dose toxicity studies are of no concern for single dose administration.

Mifepristone's activity as an abortifacient was clearly shown in several animal species. After stopping drug treatment, there was no negative effect on subsequent fertility. Peri- and post natal studies showed no effect of mifepristone on reproduction function of offspring of treated dams.

Mifepristone was not genotoxic in a range of in vitro and in vivo tests.

In rats and mice there was no teratogenic effect of the drug. In two studies in rabbits, there were scattered malformations of the encephalon in treated animals and one malformation in a control rabbit. Although there was no dose-response relationship, the sponsors state that the association

with the drug is suspect primarily because another study reported in the literature (Jost A., C.R. Acad. Sci. 303:281-284, 1986) described similar malformations of the cranium of rabbits.

The preclinical safety studies demonstrate that mifepristone is relatively nontoxic, is not genotoxic and does not adversly affect fertility or the offspring of treated mice or rats. There is a possibility that mifepristone is teratogenic in rabbits, probably secondary to its effect on the pregnant uterus.

Misoprostol (PGE_1)
Its toxicology is confined largely to an increase in normal gastric epithelial cells in mice, rats and dogs and hyperostosis after long-term treatment in mice. It is not genotoxic. In reproduction studies, misoprostol increased pre- and post-implantation losses and decreased the number of live pups. There was no fetotoxic or teratogenic effect in rats or rabbits. However, other studies with PGE_1 have revealed a dose related increase in fetal malformations in rats.

LABELLING

The labelling is satisfactory as submitted.

RECOMMENDATIONS

Pharmacology recommends approval of mifepristone for the termination of pregnancy.

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Table # 1
Embryotoxicity Study in Mice
Study Reference Number: 86/200/TX

Examination of Fetuses

Group	1	2	3	4
Dosage (mg/kg/day)	0	0.5	1.0	2.0
External Examination -				
Number of Fetuses Examined/Affected* (%)	294/11 (4)	57/5 (2)	116/3 (3)	0/0
Anomalies				
Flexion of the paws	6	3	1	0
Hematomas	1	1	1	0
Malformations				
Micrognathia	0	0	1	0
Exencephaly	3	1	0	0
Palpebral opening	0	1	0	0
Coelosomy	1	0	0	0
Internal Examination -				
Number of Fetuses Examined/Affected* (%)	148/3 (2)	130/5 (4)	58/1 (2)	0/0
Variations				
Dilation of pelvis and upper ureter	0	4	0	0
Anomalies				
Highly hemorrhagic kidney	1	1	0	0
Malformations				
Cleft palate	1	0	1	0
Situs inversus of stomach	1	0	0	0
Skeletal Examination -				
Variations				
Number of Fetuses Examined/Affected* (%)	146/110 (75)	126/105 (83)	58/53 (91)	0/0
Incomplete ossification				
Cranium (fontanelles)	9	10	6	0
Sternum	29	38	21	0
Vertebrae	12	5	3	0
Paws	102	99	47	0
Supernumerary ribs	18	17	9	0
Anomalies				
Number of Fetuses Examined/Affected* (%)	146/5 (3)	126/2 (2)	58/3 (5)	0/0 (0)
No ossification - Paws	4	0	1	0
Incomplete ossification				
Cranium (supra-occipital bone)	2	1	0	0
Fused ribs	0	1	1	0
Floating ribs	0	0	1	0
Reduced ribs	0	0	1	0

* Some fetuses had more than one condition

Table 2
Embryotoxicity Study in the Rat
Study Reference Number: AN 86

Examination of Fetuses

Group	1	2	3	4
Dosage (mg/kg/day)	0	0.25	0.50	1.0
External Examination -				
Number of Fetuses Examined/Affected* (%)	258/5 (2)	237/1 (0.4)	262/1 (0.3)	188/1 (0.5)
Anomalies				
Flexure of hindlimb	1	1	1	0
Hematomas	2	0	0	1
Malformations				
Syndactyly on hindlimbs	2	0	0	0
Internal Examination -				
Number of Fetuses Examined/Affected* (%)	127/18 (14)	121/16 (13)	133/20 (15)	96/11 (11)
Variations				
Pelvis and ureter dilated	18	16	17	11
Anomalies				
Hydronephrosis	1	1	2	0
Dextrocardia and spleen atrophy	0	0	1	0
Skeletal Examination -				
Variations				
Number of Fetuses Examined/Affected* (%)	131/115 (88)	16/95 (82)	29/116 (90)	92/83 (90)
Delayed ossification				
Skull	2	0	3	2
Sternum	54	40	63	48
Vertebrae	39	41	43	38
Paws	92	84	94	66
Extra ribs	20	12	15	10
Anomalies				
Number of Fetuses Examined/Affected* (%)	115/2 (2)	95/0 (0)	116/5 (6)	92/2 (2)
Unossification				
6th sternebra	1	0	1	1
Right and left metacarpus	0	0	1	0
8th rib and vertebrae	0	0	1	0
Metatarsus	1	0	0	0
Reduced ossification				
1 thoracic center	0	0	3	0
4 thoracic centers	0	0	0	1
5 thoracic centers	0	0	1	0
Double ribs and vertebrae (11th pair)	0	0	1	0
Fused ribs	0	0	1	0

* Some fetuses had more than one condition

Table 3
Supplementary Embryotoxicity Study in Rats
Study Reference Number: 86/201/TX

Examination of Fetuses

Group	1	2
Dosage (mg/kg/day)	0	2.0
External Examination -		
Number of Fetuses Examined/Affected* (%)	280/5 (2)	49/2 (4)
Anomalies		
Flexion of right or left hind paw	5	1
Extension of hind paws	0	1
Internal Examination -		
Number of Fetuses Examined/Affected* (%)	140/23 (16)	24/4 (17)
Variations		
Dilation of pelvis and upper ureter	23	4
Malformations		
Bilateral anophthalmia	1	0
Hydrocephalus	1	0
Skeletal Examination -		
Variations		
Number of Fetuses Examined/Affected* (%)	140/119 (85)	25/20 (80)
Incomplete ossification		
Cranium	22	3
Sternum	67	12
Vertebrae (cervical)	48	10
Paws (phalanges)	93	16
Anomalies		
Number of Fetuses Examined/Affected* (%)	140/5 (4)	25/5 (20)
No ossification		
Paws (phalanges)	2	0
6th sternebrum	1	0
Incomplete ossification		
Ribs (12th right rib or 13th pair)	2	0
Vertebrae (thoracic)	0	4
Cranium (parietal and interparietal bone)	0	1
12th and 13th right ribs flexuose	0	1

* Some fetuses had more than one condition

Table 4
Embryotoxicity Study in the Rabbit
Study Reference Number: AN 87

Examination of Fetuses

Group	1	2	3	4
Dosage (mg/kg/day)	0	0.25	0.50	1.0
External Examination -				
Number of Fetuses Examined/Affected* (%)	105/1 (1)	93/1 (1)	91/1 (1)	94/1(1)
Abnormalities				
Flexion of hind paws	0	0	0	1
Malformations				
Acephaly	0	0	1	0
Exencephaly	1	0	0	0
Exencephaly + eyes open + tail & digits reduced	0	1	0	0
Internal Examination -				
Number of Fetuses Examined/Affected* (%)	53/2 (4)	47/2 (5)	47/1 (2)	45/1 (2)
Abnormalities				
Dilation of hilum of right kidney	0	0	0	1
Dilation of hilum of kidneys	2	0	0	0
Malformations				
Interventricular communication of heart	0	2	1	0
Skeletal Examination -				
Variations				
Number of Fetuses Examined/Affected* (%)	52/44 (85)	46/41 (89)	44/32 (73)	49/45 (92)
Delay in ossification				
Sternum	5	9	12	9
Skull	10	9	12	1
Paws	13	4	5	6
Supernumerary ribs	41	32	22	40
Anomalies				
Number of Fetuses Examined/Affected* (%)	52/2 (4)	46/1 (2)	44/0 (0)	49/1 (2)
Additional center between vertebrae 5 and 6	0	1	0	0
No ossification of tarsus	2	0	0	1
Malformations				
Number of Fetuses Examined/Affected* (%)	52/0 (0)	46/1 (2)	44/0 (0)	49/0 (0)
Reduction in parietal/frontal bones, distal agenesis of limbs, missing last caudal vertebrae (in animal with exencephaly)	0	1	0	0

* Some fetuses had more than one condition

Table 5
Supplementary Embryotoxicity Study in Rabbits
Study Reference Number: 86/199/TX

Examination of Fetuses

Group	1	2	3
Dosage (mg/kg/day)	0	2.0	4.0
External Examination -			
Number of Fetuses Examined/Affected* (%)	249/0 (0)	131/1 (1)	54/1 (2)
Anomalies			
Edema	0	0	1
Malformations			
Exencephaly, rt. eye open, coelosomy, torsion/flexion right hind paw	0	1	0
Internal Examination -			
Number of Fetuses Examined/Affected* (%)	126/15 (12)	63/5 (8)	27/1 (4)
Anomalies			
(a.) Atelectasis of lungs	2	1	0
(b.) Uni- or bilateral dilation of hilum of kidney	13	2	1
(c.) Combination of (a.) + (b.)	0	1	0
Malformations			
Cleft palate	0	1	0
Skeletal Examination-			
Variations			
Number of Fetuses Examined/Affected* (%)	123/98 (80)	68/60 (88)	27/26 (96)
Incomplete ossification			
Cranium	33	23	12
Sternum	13	16	6
Paws (extremities)	10	21	7
Anomalies			
Number of Fetuses Examined/Affected* (%)	123/3 (2)	68/10 (15)	27/4 (15)
No or subnormal ossification			
Heel	1	1	2
Heel + paws (digits 2nd row)	0	0	1
Body of 2nd cervical vertebrae	0	1	0
Sternebrum	0	1	0
Multiple retardation (small fetus)	0	5	0
Incomplete ossification			
Sternebra not synchronized	2	1	0
Digits of 4 paws + cervical vertebral body	0	0	1
Ribs fused (1st and 2nd ribs on right)	0	1	0
Malformations			
Exencephalic fetus: anomalies of ossification of cranial bones + interparietal bone missing	0	1	0

* Some fetuses had more than one condition

NDA 20-687
Mifepristone

JUN 23 2000

6/23/00

Pharmacology Team Leader Labeling Review

Carcinogenesis, Mutagenesis, Impairment of Fertility

The sponsor removed the reference to [redacted] The data on mifepristone given to neonatal rats, 1 mg every other day, was not in the NDA review but comes from a publication, P.van der Schoot and R. Baumgarten, J. Reprod. Fert. 90:255-266, 1990.

Pregnancy

The sponsor addressed the question about pregnancy category by omitting reference to a particular category. The categories as currently written do not address drugs of this type that are intended for use in pregnancy and are intended to do harm to the fetus. I agree with the sponsors decision not to use any category. The statement that mifepristone is intended for termination of pregnancy and has no other use during pregnancy is logical and the meaning is clear.

The remainder of the label is acceptable as amended.

/S/ 6/23

[redacted]

NDA 20-687

[redacted]

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ON ORIGINAL

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Draft

Labeling