

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

PHARMACOLOGY REVIEW(S)

NDA 20-687
Mifepristone

9/12/00

SEP 12 2000

Pharmacology Team Leader Labeling Review #2

I received comments from [redacted] on the mifepristone label dated 9/6/00. His comments were editorial in nature with no changes to the overall assessment of the safety of mifepristone. In the second sentence of the Carcinogenesis, Mutagenesis, Impairment of Fertility section, the word [redacted] should be replaced with genotoxic and the last sentence [redacted] should be deleted.

The remainder of the label is satisfactory as written.

[redacted] /S/

[redacted]

9/12

NDA 20-687

[redacted]

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SEP 14 2000

NDA 20-687
Mifepristone

9/14/00

Pharmacology Team Leader Labeling Memo #3

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

[redacted] |S|

[redacted]

9/14

NDA 20-687

[redacted]

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ON ORIGINAL

BEST POSSIBLE COPY

/S/

JUL 22 1996

NDA 20-687

July 22, 1996

The Population Council
New York, New York

Submission: March 14, 1996

Pharmacology Review of NDA

Drug: Mifepristone; RU-486

Indication: Induction of abortion

Related IND's:

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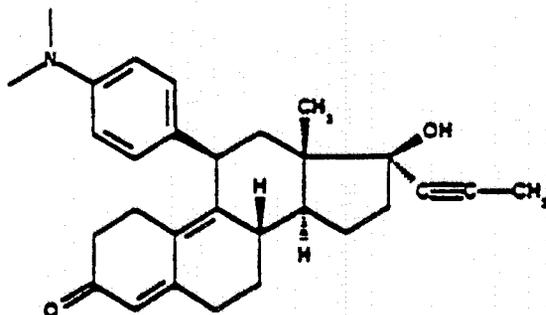
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NDA 20-687

Class: Mifepristone (RU486) is a member of the 11B-substituted norsteroid family and acts as a progestin and glucocorticoid antagonist.

Chemical name: (11B, 17B)-11-[(4-dimethylamino) phenyl]-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

Structure:

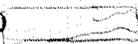


Dose: Three 200 mg tablets (600 mg) taken as a single oral dose. Two days later, unless abortion has occurred, patients will take two 200 ug tablets (400 ug) of the prostaglandin misoprostol (PGE₁).

Rationale: Mifepristone has a high relative binding affinity to the rabbit uterine progestin receptor and the rat thymus glucocorticoid receptor. In other biological tests in animals and in clinical tests in humans, mifepristone has demonstrated activity as a potent antagonist for progestins and glucocorticoids.

Progesterone is a critical hormone in mammalian reproduction and is essential for the maintenance of pregnancy. Withdrawal of the influence of the hormone in the uterus due to its competitive inhibition by mifepristone at the receptor site results in menstrual bleeding, disruption of placental function and disruption of the inhibitory effects of progesterone on the myometrial stimulatory actions of prostaglandins. These antiprogesterational activities of the drug can result in the termination of early pregnancy.

GENERAL PHARMACOLOGY

For details, see original review of IND 

The in vitro relative binding affinity (RBA) of RU486 to various receptors was compared to the natural ligands.

Rabbit uterine progesterone receptor - RBA increased during a 24 hr incubation from 0.8 to 5

times that of progesterone.

Adrenalectomized rat thymus glucocorticoid receptor - RBA was 3 times that of dexamethasone.

Castrated rat prostate androgen receptor - RBA was % of that of testosterone.

Adrenalectomized rat kidney mineralocorticoid receptor - essentially no binding compared to aldosterone.

Mouse uterine estrogen receptor - essentially no binding compared to estradiol.

Antiprogestosterone activity

In vitro, 10^{-7} M RU486 totally antagonized the effect of progesterone on LH release from LHRH stimulated rat pituitary cells.

In vivo, in the estradiol-primed immature rabbit, RU486 had no progestogen activity at 50 mg/kg and inhibited progesterone induced endometrial proliferation by 50% at a dose of 3 mg/kg. Similar studies with similar results were done in the rat and mouse.

In the pregnant rat, RU486 given at an oral dose of 10 mg/kg caused abortion in all animals treated throughout gestation except on days 1, 2 or 15.

SPECIAL PHARMACOLOGY STUDIES

For details, see original review of IND

Mifepristone was evaluated in an variety of standard pharmacological tests.

CNS activity - Only effect noted was a potentiation of the hexobarbital sleeping time in rodents with oral doses of 10-100 mg/kg.

Autonomic nervous system activity - In vitro, mifepristone antagonized acetylcholine, histamine and serotonin in the isolated guinea pig ileum at a concentration of 10^{-4} M.

Cardiovascular/respiratory activity - No effects were seen at doses up to 10 mg/kg.

Gastrointestinal activity - No effects at doses up to 100 mg/kg.

Genitourinary activity - RU486 decreased sodium excretion at doses of 10-100 mg/kg; potassium at 30-100 mg/kg and the sodium/potassium ratio. Urine volume was increased at the 100 mg/kg dose.

Endocrine activity - In fasted rats, RU486 produced a slight hypoglycemic effect at doses of 30-100 mg/kg.

Analgesic/anti-inflammatory activity - No effects at doses up to 100 mg/kg.

Hematological activity - No significant effects.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION STUDIES

Pharmacokinetics of RU486 in the rat.

Tritiated RU486 was administered iv and orally at a dose of 5 mg/kg to fasted Sprague-Dawley rats. After iv administration, the $T_{1/2}$ of the terminal phase was approximately 1 hr. The volume of distribution was half the bodyweight and the clearance was 2.7 liters/hr/kg of bodyweight.

Oral absorption was approximately 75% but the systemic bioavailability was only 39%, indicating intestinal or hepatic metabolism. The C_{max} was 0.6 ug/ml and the T_{max} was 15 minutes. Excretion was almost entirely fecal and 99% of the dose was recovered in the excreta in 4 days.

Pharmacokinetics of RU486 in the monkey

Tritiated RU486 was given iv or orally to cynomolgus monkeys at a dose of 3 mg/kg. Following iv administration, the volume of distribution was twice the body wt, the plasma clearance was 1.45 liter/hr/kg, and the terminal half-time of parent compound was about 15 hrs.

After oral administration, plasma radioactivity reached a maximum at 3 hrs. The mean peak was 0.42 ug/ml. Oral absorption was about 75% but systemic bioavailability was only 15% indicating significant intestinal or hepatic metabolism. The major route of elimination was fecal; 85% of the dose was eliminated in urine or feces within 7 days.

Compared to the rat, the $t_{1/2}$ is longer in monkeys (1 vs 15 hrs) and the plasma clearance is halved. The absorption is similar in both species but its rate is slower in the monkey. The systemic bioavailability was 39% in rats compared to only 15% in monkeys.

Binding to animal and human serum proteins in vitro and in vivo systems

In vitro RU486 is highly bound to serum proteins in rat (99%), monkey (97%) and man (99%) and was not saturable over a range of concentrations including the therapeutic concentration.

In previous in vivo studies, it was noted that there was saturable high affinity binding in humans but not in animals. After several experiments, it was determined that the protein responsible for this binding difference was the alpha-1-acid glycoprotein (HAAG), a protein that apparently has

no affinity for RU486 in animals. The results demonstrate that HAAG increases the plasma concentration of RU486 (and produces nonlinear kinetics) but not the tissue concentration and the sponsor states that this binding does not affect the pharmacological activity. I am not sure this is true but it has little significance.

Study of the transplacental passage of radioactivity in the female rat after oral administration of tritiated compound.

The transplacental passage of radioactivity, representing the sum of RU486 and its metabolites, was studied by [redacted] in female Sprague-Dawley rats. [redacted] was done on days 13 and 19 of gestation, 2 and 24 hrs after oral administration of 1 mg/kg of tritiated compound. On day 13, after 2 hrs, there was little fetal exposure to RU486. Twenty-four hrs after drug administration, there was evidence of fetal necrosis, indicating that this dose had abortive activity. The normal fetuses had low levels of radioactivity. On day 19, there was more fetal uptake of RU486 particularly of the intestinal lumen and adrenal cortex.

[redacted] data demonstrate that RU486 is taken up by fetal tissues at low concentrations.

Plasma kinetics of the radioactivity and of RU486 after oral administration of tritiated compound in the rat (5 & 200 mg/kg) and in the monkey (3, 20 & 90 mg/kg).

Plasma kinetics were examined using doses used in the one month toxicity studies (toxicokinetics).

In the rat, the increase in dose decreased and prolonged the rate of absorption, although the extent of absorption was similar. Peak level was about 3 ug/ml for the parent drug and [redacted] ug/ml for total radioactivity at the high (200 mg/kg) dose. The systemic bioavailability of the 200 mg/kg dose was twice the 5 mg/kg dose (to about 80%?), probably due to saturation of clearance/metabolizing systems.

In the monkey, the increase in dose slowed and prolonged absorption. In contrast to the rat, the higher doses (20 and 90 mg/kg) reduced the extent of absorption. The C_{max} was 28 ng/ml at 3 mg/kg; 70 ng/ml at 20 mg/kg and 160 ng/ml at 90 mg/kg. The peak radioactivity for the 90 mg/kg dose was 2.20 ug/ml. The increase in dose resulted in a shifting and flattening of the dose response curve such that the 90 mg/kg dose peaked at 4 hrs and plateaued over the next 24 hrs. The systemic bioavailability was decreased due presumably to the decreased absorption.

In summary, the C_{max} of the parent compound was approximately 3 ug/ml in rats given 200 mg/kg RU486. The C_{max} in monkeys was 160 ng/ml at the 90 mg/kg dose.

Due to the variability and the kinetic profiles, the area under the curve (AUC) was difficult to model. Actual AUC's were not presented.

In humans, the C_{max} of parent drug for a 600 mg dose is 2.56 ug/ml with an AUC of 106 ug.hr/ml. Thus the exposure to the parent drug in rats (determined from C_{max}) given 200 mg/kg was only slightly greater than in humans and in monkeys given 90 mg/kg, the exposure was about 1/16 the human exposure. However, using the C_{max} of the parent drug to calculate differences in exposures is not a satisfactory method since there was much variability, some of the metabolites have activity and there was a significant plateau in plasma drug levels in both rats and monkeys at the higher doses (ie., the C_{max} underestimates the total exposure). AUC's of parent and major metabolites would have given a much more accurate estimation of the differences in exposure between the animals and humans.

Metabolism

Metabolic profiles were primarily from bile samples collected during the first 6 hrs after iv administration of 5 mg/kg RU486 in the rat and 9 mg/kg in monkeys. The corresponding biliary excretion of radioactivity accounted for 25 and 11% of the injected dose, respectively.

The sponsor provided a metabolic pathway diagram (Figure 1). In both rats and monkeys, the metabolic pathways were similar. Two primary routes, N-demethylation and 22-hydroxylation, and a secondary route (conjugation), acetylation of the primary amine resulting from N-demethylation. In the monkey, the primary metabolite excreted was the acetylated conjugate of the 22-hydroxylated primary amine (metabolite VII). The parent compound is excreted in only small amounts.

In humans, the metabolite profile has been examined by [redacted]. There are seven "possible" metabolites but only three are measurable with current assay technology which may be due to the chemistry of the metabolites or more likely, due to the fact that they are below the detection limits of the assay. The three measurable metabolites are: RU 42 633 = N-monodemethylation; RU 42 698 = terminal hydroxylation of the 17-propynyl chain; and RU 42 848 = 4-dimethylaminophenyl in position 11B. All three of these metabolites are found in rats and cynomolgus monkeys.

TOXICOLOGY

In the toxicology studies, RU486 was normally given as an aqueous suspension in 0.25% carboxymethylcellulose and 0.20% polysorbate. Control animals received vehicle alone.

Single dose toxicology

Mice, rats and dogs were given 1000 mg/kg RU486 as a single oral dose and observed for 14-21 days.

There was one death of a male rat. Rodent toxicity included arched back, ambulatory difficulties

and abdominal distension; there was moderate diarrhea and vomiting in dogs. When administered intraperitoneal to rodents, similar results were seen. When given in a micronized form, there was more toxicity, including several deaths and this form was not used in further nonclinical or clinical studies.

Repeat dose toxicology

30-day oral toxicity study of RU486 in the rat

These one month rat and monkey studies were reviewed in the original IND [redacted] review.

Ten EOPS Sprague-Dawley rats/sex/group were gavaged with vehicle, 8, 40 or 200 mg/kg daily for 30 days.

There was no mortality. There was a moderate reduction in bodyweight gain in HD males. There was a decrease in chloride and cholesterol in males, glucose in females and albumin and alk phos in both. There was an increase in urea in HD males and females. Histopathology showed perilobular fatty degeneration of liver in HD females, hyperactivity of the thyroids, secretion by the mammary glands, blockade of estrus with follicular ovarian cysts. Atrophy of seminal vesicle and prostate epithelium at HD.

30-day oral toxicity study of RU486 in the monkey

Three cynomolgus monkeys/sex/group were gavaged with vehicle, 4, 20 or 100 mg/kg RU486 daily for 30 days.

Two HD males and one HD female were sacrificed moribund at about two weeks with vomiting, diarrhea, reduced appetite, body wt loss. Pre-terminal blood exam showed increase urea and cortisol; increased erythrocyte sedimentation rate in 2 and increased met-Hb in the 3rd. Two had high creatinine and low chloride. These effects were seen to a lesser degree in the surviving HD and some MD animals. The only histopathological finding was an increased width and eosinophilia of cells of the adrenal zona fasciculata in MD and HD males and females.

26-week oral toxicity study of RU486 in rats. RSL 613/84260. [redacted]

Twenty male and 20 female Charles River CD rats/group were gavaged with vehicle (1% methylcellulose) or 5, 25, or 125 mg/kg RU486 daily for 26 weeks.

Mortality: None drug related.

Clinical signs: Increased salivation at 125 mkd; some at 25 and occasionally at 5. Pink swellings in urogenital region - females; dose related (0, 10, 40, 68%). Hypersensitivity to

external stimuli, mainly in MD group.

Body wts: Males at 25 and 125 mkd gained less than controls. Females - 5 and 25 mkd slightly more gain than controls and 125 mkd slightly less than controls.

Hematology: Dose dependent decrease in PCV, Hb conc and RBC count in females and in HD males. Slightly higher platelet counts in HD females. Thrombotest times were shorter than controls in HD males and females.

Clinical Chemistry: Dose dependent lower blood glucose in females. Dose dependent increase in total protein conc in males and females. HD males had higher sodium levels than controls whereas females were lower. Dose dependent increase in plasma calcium in females.

Urinalysis: MD and HD animals had increased protein in the urine and the urine had a higher specific gravity. This occurred occasionally in some LD rats. HD females had more acidic urine than controls. Both MD and HD females voided more urine than controls, due presumably to their higher water intake.

Organ weights: There were various changes in organ weights none of which seemed to be of major toxicological significance.

Histopathology: Some thymus involution probably not treatment related. Dose-related increase in centrilobular enlargement in livers of males and females. Dose-related increase in hemosiderosis in adrenals, particularly in females. Dose-related increase in foci of basophilic/dilated tubules containing colloid in kidneys of males and females, more so in females. In association with this effect, there was a glomerular hyalinization/sclerosis, with a more pronounced effect in females. Also 1/20 MD and 2/20 HD females exhibited interstitial fibrosis (none in control or low dose; or in males). Increased height of the follicular epithelium of the thyroid was seen in all HD males and females. This change was dose-related in males. A thyroid follicular adenoma was seen in one HD female. Increased cortical width in the adrenals was seen in a dose-related manner in females only. Diffuse hyperplasia of the pars anterior was seen in females in a non dose-related manner.

Effects on the reproductive system:

A reduction in spermatogenesis was seen in 4/20 HD rats but not in the MD or LD groups. A dose-related reduction in colloid of the seminal vesicles was noted in association with a reduction in height of the epithelium. A reduction in colloid was also seen in the prostate.

There was a non dose-related inhibition of estrus cyclicity with a reduction in the number of corpora lutea. There was a dose-related increase in ovarian cysts. There was a reduction in endometrial stroma in all treated groups along with dilatation of endometrial glands which was dose-related. There was a shift in the epithelial lining of the cervix/vagina with dose. Control

and LD had a pseudo-stratified columnar (control only) or keratinized stratified squamous epithelium with a surface layer of columnar epithelium whereas the MD and HD rats had predominately a keratinized striated squamous or non-keratinized striated squamous epithelium. There was a dose-related increase in distension of mammary acini and ducts in females only.

Six month oral toxicity study in cynomolgus monkeys. RSL 604/84146

Five male and five female cynomolgus monkeys/group were given by gavage, vehicle (1% methylcellulose) or 5, 15 or 45 mg/kg RU486 daily for 26 weeks.

Mortality: None

Clinical signs: Occasional salivation and vomiting, mainly at the HD. (the time of vomiting in relation to dosing varied considerably, including some animals which vomited overnight)
Menstrual activity of all dosed females ceased promptly following the start of dosing.

Bodyweight: A significant loss of weight for both sexes at the HD and some at the MD for the first few weeks of the study, then normal weight gain.

Food consumption: Same as for bodyweight above.

Water consumption: Some reduction early in the study due probably to the reduced food consumption.

Ophthalmoscopy: No treatment related effects.

Electrocardiography: No treatment related effects.

Hematology: No significant changes.

Clinical chemistry: Increased serum ACTH, reduced cholesterol and a transient rise in triglycerides in the HD animals. Increased cortisol at the MD and HD. MD and HD females generally had lower estradiol and higher LH values while all treated females had lower progesterone levels than controls.

Urinalysis: Reduced urinary excretion of potassium and chloride at all dose levels for both sexes. Reduced excretion of sodium at HD only.

Organ weights: Significantly increased kidney and adrenal weights in all treated groups of both sexes. Higher liver wts in MD and HD and lower pancreas weights at the HD (both sexes).

Histopathology: liver: increased amounts and incidence of lipofuscin not dose-related. kidneys:

Non dose-related increase in cortical scarring, cortical cysts and subcapsular foci of fibrosis. adrenals: Increased eosinophilia of zona fasciculata in HD males and females and in one MD male. HD females had increased width of zona reticularis. thyroids: increased incidence of brown pigment within the follicular epithelium in HD animals. ovaries: dilated follicles and an absence of corpora lutea were seen in most treated females. Multiple large follicles were present in 2 MD and one HD female. uterus: endometrial thinning in most treated animals. Focal mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration was seen but was not dose-related. cervix: squamous metaplasia and inflammatory cell infiltration was seen in most treated monkeys but was not dose-related. Incidence of mucosal hyperplasia was increased in MD and HD animals. vagina: moderately keratinized in treated monkeys. fallopian tubes: lumen was dilated, often markedly, in most treated females. There was marked salpingitis in one MD and one HD animal; none in control of LD. mammary glands: slight increase in degree of development. testes: all treated monkeys had a reduction of spermatogenesis.

Summary: In rats, the hematological changes appeared to be due to the antiprogesterone properties of the drug while the various minor clinical chemistry alterations appear to be due to antigluccorticoid activity. There were no observable differences in the kidneys between the 5 mkd males and the controls. The sponsor believes that the renal lesions seen in females at all doses and the males at the mid- and high dose were similar to those of spontaneous progressive glomerulonephrosis, which may reflect a premature aging due to the drug. The occurrence of prominent hemosiderosis in over half of the high dose females, also showing a marginal anemia, appears to be drug related.

A variety of changes were induced in treated monkeys which could be related to disturbances of metabolism modulated by glucocorticoids and/or changes due to an unphysiological estrogen/progesterone balance. All treated groups showed an increase in the incidence of brown pigment in the hepatocytes which the sponsor suggests may be due to an increased metabolic activity caused by RU486 but there is no direct evidence of an increase in metabolic activity. Although the incidence and severity were not dose-related, the significance of the histopathological findings of areas of cortical scarring, cortical cysts and increased incidence of subcapsular foci of fibrosis of the kidneys is unclear. Some of the changes were also observed in the controls. Nevertheless, effects of RU486 were seen in the kidneys of both rats and monkeys and could be the major toxicity resulting from chronic use. No histopathology of the kidneys was seen during the 30 day studies.

Findings with the low dose of RU486 (5 mg/kg) were largely confined to cessation of menstrual activity with consequent physiological changes in the histological appearance of the reproductive organs in females and decreased spermatogenesis in one male. Pharmacological effects were usually increased at higher doses.

In general there were no unexpected findings and the observed effects can, in general, be considered predictable consequences of the pharmacological suppression of glucocorticoid and progesterone activity.

The repeat dose toxicity studies produced toxicities in animals that have little relevance to the single dose human studies even though these toxicities occurred at parent drug exposures equal to or even less than the drug exposure patients will receive. It is constant longer term exposure that produces the hormonal and other findings seen in the animal studies.

REPRODUCTIVE TOXICOLOGY

The embryotoxic activity of mifepristone, and in particular its teratogenic potential, were tested in the rat (along with a study of the cultured embryo), the mouse and the rabbit. There was an extensive peri- and postnatal study on the potential effects of maternal treatment on the offspring of rats. Other studies examined the effects of embryo-lethal doses on teratogenic effects in surviving fetuses and the effects of RU486 in the presence of progesterone.

Mifepristone was given in aqueous solution of 0.25% carboxymethylcellulose and administered orally by gavage. Controls received the vehicle alone.

In the teratology studies, day 0 of gestation was defined either by the presence of sperm in vaginal smear performed the morning after mating (rat, mouse) or by visual observation of mating (rabbit) using males of the same strain as the females. Half the fetuses from each litter were fixed in Bouin's solution for internal exam and half were fixed and stained with alizarin red for skeletal exam.

Study of the estrous cycle in the female rat treated with RU 38 486: Post-treatment outcome and incidence on reproductive function.

RU486 was administered orally to groups of 12 female Sprague-Dawley rats for 3 wks at doses of 0, 0.3 or 1.0 mg/kg/day (nkd). After the end of treatment rats were observed for 5 wks after which they were mated with untreated males. Cycles were monitored by daily vaginal smears.

Results: The estrous cycle was disrupted at both doses within 10 days of treatment. Withdrawal of treatment resulted in gradual dose-dependent restoration of the cycle over 2 - 3 wks. Reproductive endpoints of mating, gestation, parturition, litter size, morphology of offspring, bodyweight change and survival were not affected by drug treatment.

Study of the development and fertility of young rats treated subcutaneously with a single injection on day 1 after birth.

Male and female Sprague-Dawley pups from 15 litters were injected sc 1 day after birth with vehicle, 1, 10 or 100 mg/kg RU486. On day 4, the number of offspring in each litter was reduced to 8 (4 of each sex) using a random distribution table.

The general condition and growth of the offspring was not affected by treatment. Decent of testes was normal but there was a slight delay in vaginal opening in the HD females (not significant). At the age of 11 or 15 wks, histopathology revealed no effects on the testes and activity of the seminiferous tubules. Reproductive function, assessed by mating rate and fertilizing capacity, was not affected by treatment.

Embryotoxicity study in mice.

Groups of 25 Swiss CD1 mice were gavaged with vehicle, 0.5, 1 and 2 mg/kg RU 486 from day 6 to 17 of gestation.

Clinical signs: None

Body wt: Almost complete suppression of body wt gain in the 2 mkd gp. Moderate suppression in the 1 mkd gp. Final body wts (day 18) were C-62.8; LD-58.9; MD- 48.0; HD-34.8 grams.

There was a marked dose-related increase in fetal loss. The mean rate was 21% in LD; 60% in MD and 100% at HD.

Fetal wts were normal in the survivors.

Fetal examination: There were no treatment related increases in fetal anomalies or malformations (Table 1).

Embryotoxicity study in the rat.

Groups of 25 pregnant Sprague-Dawley rats were gavaged with vehicle, 0.25, 0.50 or 1.0 mkd RU486 from day 6 to day 17 of gestation.

Clinical signs: None

Body wt: Weight gain was comparable between groups except for the HD group where there was a retardation at the end of treatment.

Six HD rats had no living fetuses at autopsy. The post-implantation loss was 34% compared to 5.8% in controls (statistically significant).

Fetal wts were equal between groups and the sex ratio was the same.

Fetal examination: There were no treatment related differences in fetal anomalies or malformations (Table 2).