PRODUCT MONOGRAPH

# NU-PENTOXIFYLLINE-SR

(Pentoxifylline)

Sustained-Release Tablets, 400 mg

Vasoactive Agent

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PRODUCT MONOGRAPH

NAME OF DRUG

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(Pentoxifylline)
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THERAPEUTIC CLASSIFICATION

Vasoactive Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Pentoxifylline is a xanthine derivative. It belongs to a group of vasoactive drugs which improve peripheral blood flow and thus enhance peripheral tissue oxygenation. The mechanism by which pentoxifylline achieves this effect has not been determined, but it is likely that the following factors are involved:

1) Pentoxifylline, as other xanthine derivatives, relaxes certain smooth muscles including those of the peripheral vessels, thus causing vasodilatation or preventing spasm. This action, however, may have a limited role in patients with chronic obstructive arterial disease when peripheral vessels are already maximally dilated.

2) Pentoxifylline improves flexibility of red blood cells. This increase in the flexibility of red blood cells probably contributes to the improvement of the ability of blood to flow through peripheral vessels (hemorheologic action). This property was seen during *in vitro* and *in vivo* experiments with pentoxifylline but the correlation between

it and the clinical improvement of patients with peripheral vascular diseases has not been determined.

3) Pentoxifylline promotes platelet deaggregation.

Improvement of red blood cell flexibility and platelet deaggregation contribute to the decrease in blood viscosity.

Pentoxifylline is almost completely absorbed after oral administration. The pentoxifylline 400 mg sustained release tablet showed an initial peak plasma pentoxifylline concentration 2 to 3 hours post-administration. The drug is extensively metabolized. Biotransformation products are almost exclusively eliminated by the kidneys.

Food intake before the administration of pentoxifylline delayed the absorption but did not decrease it.

Comparative Bioavailability

Three comparative bioavailability studies were performed using healthy human volunteers - one under fasting conditions, one after a meal, and one at steady-state. The rate and extent of absorption of pentoxifylline were measured and compared following single or multiple oral dosing of either NU-PENTOXIFYLLINE-SR or Trental®. The results from measured data are summarized as follows:

FASTING STUDY:

| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Means (%)** |
|---|---|---|---|
| | NU-PENTOXIFYLLINE-SR | Trental®* | |
| $AUC_T$ (ng·hr/mL) | 443<br>488 (49) | 434<br>460 (35) | 101.9 |
| $C_{max}$ (ng/mL) | 67.6<br>72.1 (38) | 67.4<br>70.8 (32) | 100.6 |
| $T_{max}$ (hr) | 3.26 (95) | 2.72 (114) | -- |
| $t_{1/2}$ (hr)*** | 0.72 (91) | 0.42 (90) | -- |

*Trental® (Hoechst-Roussel) was purchased at a Canadian retail pharmacy.
**Based on the least square estimate of the geometric means.
***Estimated by fitting the data to a one-compartment model.

| FOOD STUDY: | | | |
|---|---|---|---|
| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Means (%)** |
| | NU-PENTOXIFYLLINE-SR | Trental®* | |
| $AUC_T$ (ng·hr/mL) | 497<br>559 (55) | 493<br>557 (52) | 98.2 |
| $C_{max}$ (ng/mL) | 93.9<br>100 (35) | 84.4<br>92.2 (41) | 107.1 |
| $T_{max}$ (hr) | 3.27 (69) | 4.08 (68) | -- |
| $t_{1/2}$ (hr)*** | 0.85 (76) | 1.10 (91) | -- |

*Trental® (Hoechst-Roussel) was purchased at a Canadian retail pharmacy.
**Based on the least square estimate of the geometric means.
***Estimated by fitting the data to a one-compartment model.

| STEADY-STATE STUDY: | | | |
|---|---|---|---|
| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Means (%)** |
| | NU-PENTOXIFYLLINE-SR | Trental®* | |
| $AUC_T$ (ng·hr/mL) | 554<br>612 (50) | 543<br>625 (54) | 102.0 |
| $C_{max}$ (ng/mL) | 140<br>159 (55) | 125<br>138 (46) | 112.1 |
| $C_{min}$ (ng/mL) | 22.5<br>30.0 (91) | 27.5<br>32.3 (83) | 84.3 |
| $T_{max}$ (hr) | 1.81 (56) | 2.50 (54) | -- |
| Fluctuation (%) | 169 (28) | 151 (35) | -- |

*Trental® (Hoechst-Roussel) was purchased at a Canadian retail pharmacy.
**Based on the least square estimate of the geometric means.

## INDICATIONS AND CLINICAL USE

NU-PENTOXIFYLLINE-SR (pentoxifylline) is indicated for the symptomatic treatment of patients with chronic occlusive peripheral vascular disorders of the extremities. In such patients pentoxifylline may give relief of signs and symptoms of impaired blood flow, such as intermittent claudication or trophic ulcers.

## CONTRAINDICATIONS

The use of NU-PENTOXIFYLLINE-SR (pentoxifylline) is contraindicated in patients with acute myocardial infarction, patients with severe coronary artery disease when, in the physician's judgment, myocardial stimulation might prove harmful, patients with hemorrhage, patients who have previously exhibited intolerance to pentoxifylline or other xanthines such as caffeine, theophylline and theobromine and in patients with peptic ulcers or recent history thereof.

## WARNINGS

Since pentoxifylline is extensively metabolized in the liver and eliminated through the kidneys, the use of this drug is not recommended in patients with marked impairment of kidney or liver function. Patients with less severe impairment of these organs should be closely monitored during pentoxifylline therapy and they may require lower doses.

### PEDIATRIC USE

The use of pentoxifylline in patients below the age of 18 years is not recommended as safety and effectiveness have not been established in this age group.

## PRECAUTIONS

### LOW, LABILE BLOOD PRESSURE

Caution should be exercised when administering NU-PENTOXIFYLLINE-SR (pentoxifylline) to patients with low or labile blood pressure. In such patients any dose increase should be done gradually.

ELDERLY PATIENTS

Pentoxifylline should be used with caution in elderly patients as peak plasma levels of pentoxifylline and its metabolites are moderately higher in this age group. Elderly patients had a slight increase in the incidence of some adverse effects. Careful dose adjustment is therefore recommended.

USE IN PREGNANCY

Reproduction studies have been performed in rats, mice and rabbits at doses up to 23, 2 and 11 times the maximum recommended daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pentoxifylline. The drug has been shown to cross the blood-placenta barrier in mice. There is no adequate experience in pregnant women. Therefore, pentoxifylline is not recommended for women who are, or may become, pregnant unless the expected benefits for the mother outweigh the potential risk to the fetus.

USE IN NURSING MOTHERS

Pentoxifylline and its major metabolites are excreted in human milk, following a 400 mg single oral dose of pentoxifylline. The patient should be advised to discontinue nursing or to discontinue taking the drug depending on the importance of the drug to the mother.

DRUG INTERACTIONS

Antihypertensive Agents:

Pentoxifylline may potentiate the action of antihypertensive agents. Patients receiving these agents require blood pressure monitoring and possibly a dose reduction of the antihypertensive agents.

Sympathomimetics:

Combined use with other xanthines or with sympathomimetics may cause excessive CNS stimulation.

Theophylline:
Although causality has not been established, concurrent use of pentoxifylline with theophylline has resulted in elevated theophylline plasma levels, which may enhance the possibility of adverse effects.

Erythromycin:
No data are available on the possible interaction of pentoxifylline and erythromycin. However concurrent administration of erythromycin and theophylline has resulted in significant elevation of serum theophylline levels with toxic reactions.

Hypoglycemic Agents:
In patients treated with hypoglycemic agents, a moderate adjustment in the dose of these agents may be required when pentoxifylline is prescribed.

Anticoagulants:
There have been reports of bleeding and/or prolonged prothrombin time in patients treated with pentoxifylline with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin time, while patients with other risk factors complicated by hemorrhage (e.g. recent surgery) should have periodic examinations for signs of bleeding, including hematocrit and hemoglobin.

Antacids:
In patients with digestive side effects, antacids may be administered with pentoxifylline. In a comparative bioavailability study, no interference with absorption of pentoxifylline by antacids was observed.

Cimetidine:
During concurrent use of cimetidine and pentoxifylline, cimetidine has been shown to significantly increase the steady-state plasma concentration of pentoxifylline, which may enhance the possibility of adverse effects.

## ADVERSE REACTIONS

The most frequent adverse effect reported with pentoxifylline is nausea (14%). Individual signs/symptoms not marked with an asterisk occurred at an incidence below 1% (* = incidence between 1% and 3%).

### CARDIOVASCULAR SYSTEM
Flushing*, chest pain, arrhythmia, hypertension, dyspnea, edema, hypotension, angina, tachycardia.

### CENTRAL NERVOUS SYSTEM
Dizziness/lightheadedness (9.4%), headache (4.9%), drowsiness/sleepiness, tremor, agitation, anxiety, confusion, insomnia, restlessness.

### GASTROINTESTINAL SYSTEM
Nausea (14%), vomiting (3.4%), abdominal discomfort*, bloating*, diarrhea*, dyspepsia*, abdominal burning, abdominal pain, anorexia, flatus, constipation, hemorrhage, heartburn, salivation, dry mouth/throat, hepatitis, jaundice, increased liver enzymes.

### HEMIC AND LYMPHATIC
Decreased serum fibrinogen, pancytopenia, purpura, thrombocytopenia, leukopenia, anemia, aplastic anemia.

### HYPERSENSITIVITY REACTIONS
Pruritus, rash, urticaria, angioedema.

ORGANS OF SPECIAL SENSE

Blurred vision, scotoma, lacrimation, epistaxis.

MISCELLANEOUS

Malaise*, muscle aches/spasms, weight change, backache, bad taste in mouth, leg cramps, fever, weakness, sweating.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with pentoxifylline has been reported in children and adults. Symptoms appear to be dose related and usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.

In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions with intravenous diazepam. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

## DOSAGE AND ADMINISTRATION

The recommended starting dosage of NU-PENTOXIFYLLINE-SR (pentoxifylline) is 400 mg twice daily after meals. The usual maintenance dose is 400 mg twice or three times daily. A maximum dose of 400 mg three times daily should not be exceeded.

It may take up to two months to obtain full results.

NU-PENTOXIFYLLINE-SR 400 mg Tablets must be swallowed whole.

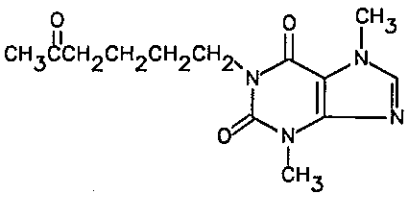
## PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Pentoxifylline

Chemical Name: 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-1 H-purine-2,6 dione

Structural Formula:



Molecular Formula: $C_{13}H_{18}N_4O_3$

Molecular Weight: 278.3

Description:

Pentoxifylline is an odourless, colourless crystalline powder with a bitter taste, soluble in water, methanol and chloroform. It has a melting point range of 101 to 106°C.

COMPOSITION

In addition to pentoxifylline, each sustained release tablet contains the non-medicinal ingredients hydroxypropyl methylcellulose, magnesium stearate, colloidal silicon dioxide, polyethylene glycol, titanium dioxide, carnauba wax and FD&C red #3.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15-30°C).

## AVAILABILITY OF DOSAGE FORMS

Each bright pink, capsule-shaped, biconvex, film-coated, sustained-release tablet identified 'NU-400' on one side, contains 400 mg pentoxifylline. Available in bottles of 100 and 500.

## PHARMACOLOGY

In dogs, 10 mg/kg i.v. pentoxifylline produced a short but significant drop in BP. 5-15 mg/kg i.v. pentoxifylline produced a dose related increase in heart rate and a decrease in peripheral resistance for 30-60 minutes. In dogs, cats, and rats, after 1-3 mg/kg pentoxifylline i.v. the blood pressure, heart rate and respiration remained practically unchanged, whereas higher doses of pentoxifylline (14-25 mg/kg i.v.) caused a transient decrease in blood pressure and an increase in heart rate. In rabbits, pentoxifylline (2-10 mg/kg i.v.) produced a dose related fall in BP. In rabbits, cats and dogs the respiration was slightly stimulated. The blood pressure response in cats and rabbits after epinephrine was slightly inhibited by pentoxifylline. The i.v. administration of pentoxifylline or aminophylline in doses of 3-10 mg/kg to cats resulted in a 20 and 35% increase in dp/dt respectively.

Femoral musculature circulation in cats, measured indirectly by heat-conduction probe, was increased by pentoxifylline (10-50 mg/kg p.o. and 1-20 mg/kg i.v.) and papaverine (1 mg/kg i.v.) while aminophylline (1-10 mg/kg i.v.) was without effect. In hepatic circulation in cat, pentoxifylline (2 mg/kg i.v.) was as effective as papaverine (1 mg/kg i.v.) in increasing blood flow.

In carotid artery blood of anesthetized cats, pentoxifylline (5 mg/kg i.v.) produced a 5.8 mmHg increase in $PO_2$ whereas papaverine, (1 mg/kg i.v.) produced a 4.0 mmHg increase,

aminophylline 3 mg/kg i.v. produced a 1 mmHg increase in $PO_2$ and 5 mg/kg i.v. reduced $O_2$ tension 1 mmHg.

Reserpine pretreatment did not influence the positive chronotropic effect of pentoxifylline in rats.

On isolated rabbit hind limb, pentoxifylline-induced vasodilation was comparable to acetylcholine-induced vasodilation at equal doses.

In isolated guinea pig heart preparation, pentoxifylline (30 - 600 $\mu$g) produced no significant effect on contractility or heart rate and small increase in coronary flow while aminophylline (30-808 $\mu$g) produced a biphasic effect on coronary flow, slight negative inotropism and no rate alteration. The activity of pentoxifylline on coronary flow was not influenced by propranolol (7.5 $\mu$g). In isolated guinea pig tracheal chain, the bronchodilator activity of pentoxifylline was significantly greater than aminophylline. The presence of propranolol $10^{-6}$ g/mL did not affect results.

Contractions induced in isolated guinea pig seminal vesicle by epinephrine were reduced by pentoxifylline and by aminophylline in the same concentration range.

Bronchospasm induced by i.v. acetylcholine in guinea pigs was inhibited by 97%, and that induced by i.v. histamine inhibited by 100%, at pentoxifylline doses of 50 mg/kg i.v. and 20 mg/kg i.v. respectively.

On rabbit aorta strip preparation both pentoxifylline and aminophylline inhibited the NE-induced contraction.

The histamine-induced increase of capillary permeability in rats was not influenced by 10 or 25 mg/kg pentoxifylline i.p.

Pentoxifylline given orally (25-100 mg/kg) to rats had no influence on blood sugar, while in rabbits given i.v. (10-50 mg/kg) the higher dose pentoxifylline increased blood sugar from 100 to 187 mg% at 1 hour post-dosing.

In comparison to aminophylline, the central stimulatory effect of pentoxifylline in rats was significantly milder. Pentoxifylline (40 and 200 mg/kg, p.o.) did not prevent convulsions induced by nicotine in mice. Pentoxifylline does not influence significantly the motility of mice and rats, food consumption of rats, sleeping time after hexobarbital in rats and mice, ptosis, sedation and hypothermia of mice caused by reserpine, catalepsy in rats induced by perphenazine, or fighting behaviour in mice. It has no anticonvulsive, anti-inflammatory, and local anaesthetic activity and exhibits only a slight analgesic, choleretic, diuretic and antitussive effect.

The results of *in vitro* studies in which pentoxifylline was added to blood from human volunteers, and *in vivo* studies in which pentoxifylline was given orally or intravenously to patients with peripheral vascular disease indicate that pentoxifylline can improve impaired erythrocyte flexibility. The possible mechanisms involved in this effect are most likely related to intracellular adenosine triphosphate (ATP) inasmuch as ATP depleted cells have reduced flexibility and vice versa. Pentoxifylline raises erythrocyte intracellular ATP concentrations. In another *in vitro* study using rat erythrocytes, pentoxifylline has been shown to decrease intracellular $Ca^{++}$ concentrations and increase phosphorylation of the proteins in the erythrocyte membrane by facilitating $Mg^{++}$ dependent phosphoprotein phosphatase and transglutaminase activity. This results in an increased membrane phosphoprotein concentration which is believed to increase red blood cell flexibility.

In an *in vivo* rat study designed to test platelet deaggregation properties of drugs, pentoxifylline at doses of 3, 6 and 12 mg/kg i.v. reduced platelet aggregation to "sticky" cancer cells (Walker 256 carcinosarcoma) and inhibited their attachment to endothelium. Monkeys given pentoxifylline 6, 12, 18 and 24 mg/kg i.v. exhibited dose related reduction in platelet aggregation index. In humans, pentoxifylline inhibits ADP-stimulated platelet aggregation as measured by the Born method.

Epinephrine-induced lipolysis (rat epididymal adipose tissue) was increased by pentoxifylline and aminophylline at $10^{-3}$ and $10^{-4}$ M *in vitro*. *In vivo*, epinephrine-induced glycerine production (same tissue) was significantly inhibited by both compounds (10 mg/kg/i.p.) and FFA was decreased.

Pharmacokinetics:

Beagle dogs were given 3.0 mg/kg p.o. pentoxifylline-$^{14}$C and radioactivity measured in plasma and body tissues. Mean maximal blood levels (2.1 $\mu$g/mL) were reached 1 hour post-dosing. Plasma concentration/time curve displayed a biphasic elimination profile with $t_{½}$ 0.8 hours and 30 hours. Over 80% of the radioactivity was found in urine within 24 hours. At maximal blood levels time, highest concentrations were found in the gallbladder (110.0 $\mu$g/g), kidney, liver and bladder (4.8 $\mu$g/g); lowest concentrations were found in brain (0.40 $\mu$g/g), fat, heart and gonads (1.3 $\mu$g/g).

## TOXICOLOGY

### ACUTE

| Species | Route | $LD_{50}$ (mg/kg) |
|---|---|---|
| Mouse | p.o.<br>i.v.<br>i.p. | 1385<br>197<br>239 |
| Rat (SD) | p.o.<br>i.v. | 1772<br>231 |

Toxicity was characterized by hypersalivation in orally dosed animals, increased or irregular respiration, tonic-clonic convulsions and paresis.

Rabbits survived 50 mg i.v.; signs and symptoms of toxicity were similar to those seen in rats. Dogs survived 160 mg i.v. and 320 mg p.o. They showed aggression and ataxia after oral dosing and aggression, fear, vomiting, diarrhea after i.v. dosing.

### SUBACUTE AND CHRONIC TOXICITY

Mouse, i.v., 14 Days:

Groups of 8 female 12 week old mice were given daily doses of 0, 12.5, 25, 50 or 100 mg/kg of pentoxifylline. One mouse of the highest dosage group died after 6 days. Death was preceded by dyspnea and clonic convulsions. The other animals of this group showed a decrease in spontaneous activity and had their eyes closed.

Mouse, p.o., 78 Weeks:

Four groups of 20 males and females were given pentoxifylline in diet at 0, 50, 150 or 450 mg/kg/day. Five animals per sex per group were killed after 26 weeks and another 5 at 52 weeks. After 78 weeks the remaining animals were observed for 13 weeks, without exposure to the compound. High dose males showed a greater frequency of bronchiectasis, renal cysts, testicular

atrophy, urinary bladder dilatation and bone marrow hyperplasia than controls. High dose females showed a greater frequency of bronchiectasis, fatty degeneration of the liver, fatty degeneration/amyloidosis in the kidneys, splenic hyperplasia, hyperplasia and fibrosis of bone marrow and osteoporosis than controls.

There was an increased incidence of benign ovarian and uterine tumours, and angiosarcoma of the liver was observed in 1 animal of each sex in the high dose group.

Rat, i.v., 14 Days:
Groups of 10 females were given pentoxifylline at daily doses of 0, 12.5, 25, 50 or 100 mg/kg. Four of the 10 rats given 100 mg/kg showed depressed spontaneous activity, staggering gait, closed eyelids, salivation and clonic and tonic convulsions and died. There were pulmonary hemorrhages in these 4 rats.

Rat, i.v., 30 Days:
Groups of 10 males and 10 females were given pentoxifylline in doses of 0, 10, 25 or 50 mg/kg/day. There was a slight decrease in cholesterol and esterified cholesterol in the 25 and 50 mg/kg male groups and a slight increase in the mean blood glucose level in the 25 and 50 mg/kg female groups. Perilobular hyaline droplet degeneration of the liver occurred in all groups, but appeared to be more severe in the male rats of the two highest dosage groups.

Females on top dose displayed increased incidence of renal tubule calcification.

Rat, p.o., 78 Weeks:
Groups of 70 males and 70 females were given pentoxifylline in their diet at 0, 50, 150 or 450 mg/kg/day. Five animals per sex per group were killed at 52 weeks and another 5 at 78 weeks. After 78 weeks, the remaining animals were observed for 26 weeks without additional exposure to pentoxifylline. In the

middle-dose group, the body weight gain was significantly decreased; at the end of the 6-month follow-up period the body weights were normal. In the high-dosage group the body weight gain was decreased. At the end of the 6-month follow-up period the female weights had returned to normal but the males had not. The mortality rate was significantly increased for the males in the high-dose group. The cause of death was similar in treated and untreated animals, but in the treated animals there was an increase in congestive streaks of the liver, cardiosclerosis and scars in the heart, dilatation of the uterus, and thyroid atrophy (females only). There were more interstitial cell tumours of the testicles in the high dosage group but the difference was not significant. There was a significant increase in fibroadenomas of the mammary gland (females) in the high dose group.

Dog, i.v., 30 Days:
Groups of 3 male and 3 female beagles were given pentoxifylline in doses of 0, 10, 25 and 63 mg/kg 5 days/week for 6 weeks. There was licking of the lips, vomiting, incoordination, uneasiness and dose-related heart rate increase following the injection. Some tubular renal degeneration occurred at 25 and 63 mg/kg. There was also congestion of liver at these doses and congestion of spleen at the highest dose.

Dog, p.o., 1 Year:
Groups of 3 male and 3 female beagles were given pentoxifylline in doses of 0, 32, 100, 320 or 400 mg/kg/day. There was incoordination, salivation and altered temperament following drug administration. Deaths occurred at doses of 320 and 400 mg/kg due to extensive or focal pulmonary edema and hemorrhages, and marked congestion in mucosa of the intestinal tract. Acetone was detected in urine at 2 weeks to 26 weeks in some dogs of the 3 highest dose groups. At 52 weeks acetone was no longer detected. Giant cell formation in the testicles was

observed in 2 dogs which died in the 320 mg/kg group. Granuloma in the lymph nodes occurred in 1 dog of the control group, and 2 in the 320 mg/kg group.

REPRODUCTION AND TERATOLOGY

Mouse, i.v.:

Mice were given 0, 12.5, 25 or 50 mg/kg pentoxifylline from day 15 of gestation through day 21 of lactation. Between days 21 and 23 all the animals were killed. Some of the $F_1$ offspring were reared and mated. The females and $F_2$ offspring were raised to weaning, and then killed. All other $F_1$ offspring were killed at 10 weeks. There was no significant effect on pregnancy and on the fetal development.

Rat, p.o.:

Groups of 10 males and 20 females were given 0, 57, 170 or 570 mg/kg/day pentoxifylline for 10 weeks before mating and then continuously through gestation and lactation. Fifty percent of the females were killed on the 13th day of gestation and the remaining animals were allowed to raise their young to weaning.

The number of resorptions, particularly early resorption, was greater in the high dose group. The number of young reared to weaning was lower for the high dose group.

Rat, p.o. and i.v.:

Groups of 20 females were given pentoxifylline 0, 57, 100 or 570 mg/kg orally or 0.8, 3.2 or 12.5 mg/kg i.v. from the 6th or 7th day to the 16th day of gestation. Two control groups were used in the i.v. study. One group was given a volume of physiological NaCl similar to the treatment groups and the other group was not treated at all. On the 20th day of pregnancy the fetuses were removed by Caesarean section. There was a significant reduction in the number of fetuses in the highest oral dosage group and the number of resorption sites was increased. There were no fetal abnormalities. The highest i.v.

dose caused a slight reduction in number of fetuses and increase in resorption.

Rat, p.o.:
Groups of 20-24 pregnant animals were given pentoxifylline 0, 57, 170 or 570 mg/kg by stomach tube from day 17 of gestation to day 21 postpartum. Between days 21 and 23, all animals were killed. There were no drug effects.

Rabbit, i.v. and p.o.:
Groups of 10 pregnant females were given pentoxifylline at 0, 0.26, 5.80 or 265 mg/kg/day orally or 1.0, 3.2, or 10 mg/kg i.v./day. There were no drug effects.

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