PRODUCT MONOGRAPH

Pr ratio-PENTOXIFYLLINE
(pentoxifylline)

400 mg Sustained-Release Tablets

Vasoactive agent

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Date of Revision:
September 18, 2009

Submission Control No: 131604

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Pratio-PENTOXIFYLLINE

(pentoxifylline)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Sustained release tablet 400 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Pratio-PENTOXIFYLLINE is indicated for the symptomatic treatment of:

- patients with chronic occlusive peripheral vascular disorders of the extremities;

In such patients Pratio-PENTOXIFYLLINE may give relief of signs and symptoms of impaired blood flow, such as intermittent claudication or trophic ulcers.

CONTRAINDICATIONS

The use of Pratio-PENTOXIFYLLINE is contraindicated in:

- Patients who are hypersensitive to pentoxifylline or other xanthines such as caffeine, theophylline and theobromine or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with acute myocardial infraction;
- Patients with severe coronary artery disease when, in the physician's judgement, myocardial stimulation might prove harmful;
- Patients with hemorrhage (e.g. extensive retinal bleeding) or at risk of increased bleeding;
- Patients with peptic ulcers or recent history thereof.

WARNINGS AND PRECAUTIONS

General

Patients with hepatic impairment should be closely monitored during Pratio-PENTOXIFYLLINE therapy and may require lower doses. Pratio-PENTOXIFYLLINE is extensively metabolized in the liver, the use of this drug is not recommended in patients with severe hepatic impairment of liver function (Child-Pugh class C, score > 9).

Patients with renal impairment (creatinine clearance below 80 mL/min) should be closely monitored during Pratio-PENTOXIFYLLINE therapy and may require lower doses. Since Pratio-PENTOXIFYLLINE is eliminated through the kidneys, the use of this drug is not recommended in patients with severe renal impairment (creatinine clearance below 30 mL/min).

Cardiovascular

Low, labile blood pressure: Caution should be exercised when administering Pratio-PENTOXIFYLLINE to patients with low or labile blood pressure. In such patients any dose increase should be done gradually.

Hematologic

The administration of Pratio-PENTOXIFYLLINE has been associated with bleeding and/or prolonged prothrombin time (see DRUG INTERACTIONS). The risk of bleeding may be increased by combined treatment with anticoagulant agents or use in coagulation disorders. Therefore, in patients with coagulation disorders or being treated with anticoagulant therapy, Pratio-PENTOXIFYLLINE should be used with caution and only, when in the physician's judgement, the potential benefit outweighs the risk.

Special Populations

Pregnant Women

Reproduction studies have been performed in rats, mice and rabbits at doses up 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, Pratio-PENTOXIFYLLINE is not recommended for women who are, or may become, pregnant unless the expected benefits for the mothers outweigh the potential risk to the fetus.

Nursing Women

Pentoxifylline and its major metabolites are excreted in human milk, following a 400 mg single oral dose of Pratio-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.

Pediatrics

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

Geriatrics

Pratio-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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The most frequent adverse event reported with Pratio-PENTOXIFYLLINE is nausea (14%). Individual signs/symptoms listed in the table below occurred at an incidence between 1 and 3%, except when stated otherwise.

	Symptoms
Body as a whole	Malaise
Cardiovascular system	Flushing
Central nervous system	Dizziness/light-headedness (9.4%), headache (4.9 %)
Gastrointestinal system	Nausea (14%), vomiting (3.4%), abdominal discomfort, bloating, diarrhea, dyspepsia

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Body as a whole: Muscle aches/spasm, weight change, backache, bad taste in mouth, leg cramps, fever, weakness, sweating.

Cardiovascular: Chest pain, arrhythmia, hypertension, dyspnea, edema, hypotension, angina, tachycardia.

Central nervous system: Drowsiness/sleepiness, tremor, agitation anxiety, confusion, insomnia, restlessness.

Gastrointestinal: Abdominal burning, abdominal pain, anorexia flatus, constipation, haemorrhage, heartburn, salivation, dry mouth/throat, hepatitis, jaundice, increased liver enzymes.

Hemic and lymphatic: Decreased serum fibrinogen, pancytopenia, purpura, thrombocytopenia, leucopenia, anemia, aplastic anemia.

Hypersensitivity reactions: Pruritis, rash, urticaria, angioedema.

Organs of special sense: Blurred vision, scotoma, lacrimation, epistaxis.

Post-Market Adverse Drug Reactions

Hepatobiliary disorders: Intrahepatic cholestasis.

Immune system disorders: Severe anaphylactic/anaphylactoid reaction with, for example, angioneurotic edema, bronchospasms, sometimes shock.

Infections and infestations: Aseptic meningitis.

Investigations: Transaminase elevation.

Psychiatric: Sleep disturbances.

Skin and subcutaneous tissue disorders: Reddening of skin.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Antihypertensive agents: Pratio-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.

Anticoagulants: There have been reports of bleeding and/or prolonged prothrombin time in patients treated with Pratio-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 haemoglobin.

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.

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

Hypoglycemic agents: The blood-sugar lowering effect of insulin or oral antidiabetic agents may be potentiated. In patients treated with hypoglycemic agents, a moderate adjustment in the dose of these agents may be required when Pratio-PENTOXIFYLLINE is prescribed.

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.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal product have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyles have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended starting dosage of ratio-PENTOXIFYLLINE is 400 mg twice daily after meals. The usual dose is 400 mg twice or three times daily. A maximum of 400 mg three times daily should not be exceeded.

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

Pratio-PENTOXIFYLLINE 400 mg sustained release tablets must be swallowed whole.

OVERDOSAGE

Overdosage with Pratio-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. Initial manifestations of acute overdose with pentoxifylline may be nausea, dizziness, tachycardia, fever, gastrointestinal bleeding – coffee-ground vomiting and areflexia. The highest amount ingested was 80 mg/kg with which flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation have been observed. All patients recovered.

No specific antidote is known. 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 absorb pentoxifylline in patients who have overdosed.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pratio-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 Pratio-PENTOXIFYLLINE achieves this effect has not been determined, but it is likely that the following factors are involved:

- Pratio-PENTOXIFYLLINE, as with 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.
- Pratio-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 (haemorheologic action). This property was seen during *in vitro* and *in vivo* experiments with Pratio-PENTOXIFYLLINE but the correlation between it and the clinical improvement of patients with peripheral vascular diseases has not been determined.

- Pratio-PENTOXIFYLLINE promotes platelet deaggregation.

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

Pharmacokinetics

Pentoxifylline is almost completely absorbed after oral administration. The Pratio-PENTOXIFYLLINE 400 mg sustained release tablet showed an initial peak plasma pentoxifylline concentration 2 to 3 hours post-administration. The drug is extensively metabolized. The active main metabolite 1-(5-hydroxyhexyl)-3,7-dimethyl-xanthine (metabolite I) is measurable in twice the concentration in plasma of that of its parent substance. Biotransformation products are almost exclusively eliminated by the kidneys.

Food intake before the administration of Pratio-PENTOXIFYLLINE delayed the absorption but did not decrease it.

STORAGE AND STABILITY

Store at room temperature (15 to 30 °C). Protect from light.
Protect from moisture and excessive heat.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Pratio-PENTOXIFYLLINE sustained release tablets 400 mg contain 400 mg medicinal ingredient, pentoxifylline.

The qualitative formulation of Pratio-PENTOXIFYLLINE tablets is: pentoxifylline, benzyl alcohol, FD&C red no.3, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 8000, povidone, talc, titanium dioxide.

Availability

Pratio-PENTOXIFYLLINE is available as 400 mg, pink, oblong, film-coated, sustained release tablets, one face is embossed with "Pentox", the other face is embossed "Alti", packed in bottles of 100 and 500 Tablets and packed in unit Pack boxes of 60 [4x15 clear PVC film and aluminium foil blister-packed] tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

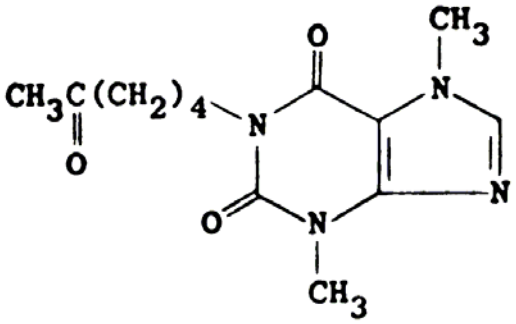
Proper name: pentoxifylline

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

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

Molecular mass: 278.3

Structural formula:



Description: Pentoxifylline is a white to creamy white, crystalline powder. It is freely soluble in chloroform and methanol, soluble in water, sparingly soluble in ethanol and slightly soluble in ether. It has a melting point of 104°C to 107°C, within a 3°C range.

DETAILED PHARMACOLOGY

In vitro and *in vivo* Animal Data

Pharmacodynamics

In dogs, 10mg/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 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 on dp/dt respectively.

Femoral musculature circulation in cat, 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 anaesthetized cat, 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. reduce O_2 tension 1mmHg.

Reserpine pre-treatment did not influence the positive chronotropic effect of pentoxifylline in rats.

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

In isolated guinea pig heart preparation, pentoxifylline (30-600 μg) produced no significant effect on contractility or heart rate and small increase in coronary flow while aminophylline (30-808 μg) 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 propanolol (7.5 μg). In isolated guinea pig tracheal chain, the bronchodilator activity of pentoxifylline, was significantly greater than aminophylline. The presence of propanolol 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 of fighting behaviour in mice. It has no anticonvulsive, anti-inflammatory and local anaesthetic activity and exhibits only a slight analgesic, cholorectic, 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 mechanism 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 erythrocytes 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 erythrocytes 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 human 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.v.) 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 μg/mL) were reached 1 hour post-dosing. Plasma concentration/time curve displayed a biphasic elimination profile with $t_{1/2}$ 0.8 hours and 30 hours. Over 80% of the radioactivity was found in urine within 24 hours. At maximal blood levels time, highest concentration was found in gallbladder (110.0 μg/g), kidney, liver and bladder (4.8 μg/g): lowest concentrations were found in brain (0.40 μg/g), fat, heart and gonads (1.3 μg/g).

TOXICOLOGY

Acute Toxicity

ACUTE TOXICITY (LD_{50}) OF PENTOXIFYLLINE

SPECIES	ROUTE	LD_{50}(MG/KG)
Mouse	p.o	1385
	i.v.	197
	i.p	239
Rat (SD)	p.o	1772
	i.v.	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 the 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 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 months follow-up period the body weight were normal. In the high-dosage group the body weight gain was decreased. At the end of the 6 months follow-up period the female weight 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, cadiosclerosis 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 5days/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 oedema 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 in 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 13^{th} 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 6^{th} or 7^{th} day to the 16^{th} 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 570mg/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, 26.5, 80 or 265 mg/kg/day orally or 1, 3.2, 0r 10 mg/kg/i.v./day. There were no drug effects.

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21. Product Monograph **Pr TRENTAL®** (pentoxifylline sustained release tablets, 400 mg Mfr. Std.). Date of revision December 16, 2008. sanofi-aventis Canada Inc.

PART III: CONSUMER INFORMATION

Pratio-PENTOXIFYLLINE
Pentoxifylline Sustained Release Tablets

This leaflet is part III of a three-part "Product Monograph" published for Pratio-PENTOXIFYLLINE and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Pratio-PENTOXIFYLLINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Pratio-PENTOXIFYLLINE has been prescribed to you by your health provider to treat your chronic vascular (blood flow) disorders in your extremities (legs and arms).

What it does:

Pratio-PENTOXIFYLLINE belongs to a group of medicines known as vasoactive drugs which improve peripheral blood flow and thus enhances peripheral tissue oxygenation.

When it should not be used:

Do not use **Pratio-PENTOXIFYLLINE** if:

- You are allergic to it or other xanthine such as caffeine, theophylline and theobromine and to any of the components of its formulation.
- You have any heart disease
- You have uncontrolled bleeding or are at risk of such
- You have peptic (stomach) ulcers

What the medicinal ingredient is:

Pentoxifylline

What the important nonmedicinal ingredients are:

Benzyl alcohol, FD&C red no.3 (colouring agent), hydoxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 8000, povidone, talc, titanium dioxide.

What dosage forms it comes in:

Sustained released tablets of 400 mg

WARNINGS AND PRECAUTIONS

BEFORE you use **Pratio-PENTOXIFYLLINE** talk to your health provider if:

- You have liver disease or disorder
- You have kidney disease or disorder
- You have coagulation disorder
- You are pregnant
- You are a nursing mother
- You have low or labile blood pressure

Almost all patients can drive or operate machinery while taking **Pratio-PENTOXIFYLLINE**, but you should not perform these tasks, which may require attention, until you know how you tolerate your medicine.

INTERACTIONS WITH THIS MEDICATION

Sometimes drugs can interact with other drugs, so tell your doctor or pharmacist if you are taking any other medications, including prescription, non-prescription and natural health products. In particular, tell your doctor if you are taking any of the following:

- Drugs to reduce blood pressure (eg. ACE inhibitors, angiotensin II receptor antagonist)
- Sympathomimetics (eg amphetamines)
- Medication for asthma (eg. theophylline)
- Medication for diabetes
- Anticoagulants (eg. heparin, warfarin)
- Erythromycin (an antibiotic)
- Medication to treat ulcers (eg. cimetidine)

PROPER USE OF THIS MEDICATION

This drug is specifically prescribed for you. Do not give it to others, even if they have the same symptoms, and you yourself must not use it for any condition other than the one for which it was prescribed.

It is important that you take **Pratio-PENTOXIFYLLINE** as prescribed by your doctor.

Usual dose:

Usually your doctor will prescribe **Pratio-PENTOXIFYLLINE** tablets at a dose of 400 mg twice or three times daily, which will be individualized based on your condition.

A maximum of 400 mg three times daily should not be exceeded.

Swallow the tablets whole with a glass of water after meals. You should always respect the prescribed interval between the doses. Never change the dose of **Pratio-PENTOXIFYLLINE** you are taking unless your doctor tells you to.

Overdose:

If you have accidentally taken too much **Pratio-PENTOXIFYLLINE** contact your doctor or nearest hospital emergency department immediately, even if you do

not feel sick. If you go to the doctor or the hospital, take the **Pratio-PENTOXIFYLLINE** container with you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its beneficial effects, **Pratio-PENTOXIFYLLINE** like all other drugs, may sometimes cause undesirable effects. The most frequent ones are:

- nausea, vomiting,
- headache, dizziness (light-headedness),
- abdominal discomfort,
- bloating,
- diarrhoea,
- dyspepsia (heart burns) and
- flushing, and
- malaise

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic reaction or skin reaction (itching, swelling, red spots and blisters).			✓
Uncommon	Chest pain.			✓
Uncommon	Difficulty breathing.			✓
Uncommon	Abnormal bleeding (bleeding around your eyes or blood in your stool).			✓

This is not a complete list of side effects. For any unexpected effects while taking **Pratio-PENTOXIFYLLINE**, contact your doctor or pharmacist.

HOW TO STORE IT

Store your tablets at room temperature (15° – 30°C). Protect from light. Protect from moisture and excessive heat.

There is an expiration date on the label. Do not use the medicine after this date.

Return any leftover tablets to the pharmacist, unless the doctor tells you to keep them at home.

As with all medicines, keep **Pratio-PENTOXIFYLLINE** out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect .

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor,

ratiopharm inc.
17 800 Lapointe, Mirabel
Quebec, Canada, J7J 1P3
1-800-337-2584

Last revised: September 18, 2009