NEW ZEALAND DATA SHEET

1. TRENTAL 400 MG MODIFIED RELEASE TABLETS

Trental 400 mg modified release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pentoxifylline 400 mg.

Oxpentifylline and Pentoxifylline are interchangeable and refer to the same molecule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablet.

Oblong, pink, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trental is indicated in the treatment of peripheral occlusive vascular disease and circulatory disorders of arteriosclerotic, diabetic, inflammatory or function origin; trophic disorders (e.g., leg ulcers and gangrene).

Circulatory disorders in the eye and ear associated with degenerative vascular processes resulting in a decrease of visual and auditory function.

4.2 Dose and method of administration

Dose

The usual dosage of Trental in controlled release tablet form is one tablet (400 mg) three times a day with or after meals, to be swallowed whole with some liquid. While the effect of Trental may be seen within 2-4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double blind clinical studies of 6 months duration.

Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that dosage be lowered to one tablet twice a day (800mg/day). If side effects persist at this lower dosage the administration of Trental should be discontinued.

In patients with low or labile blood pressure, or with renal or hepatic dysfunction, an individual dosage adjustment is required. This also applies to patients with renal dysfunction (creatinine clearance of less than 30 mL/min) where, according to individual tolerance, a dosage adjustment of 30 to 50% may be necessary.

Paediatric population

Trental is not recommended for children.

Method of administration

Oral administration.

Tablets should be taken with or immediately after meals, and swallowed whole with some liquid.

4.3 Contraindications

Patients who have previously exhibited intolerance to this product; other methylxanthines, such as caffeine, theophylline and theobromine; or any of the excipients of Trental listed in section 6.1.

Trental should not be given to patients with severe haemorrhage, eg. massive retinal haemorrhage, cerebral haemorrhage, acute myocardial infarction or patients with peptic ulcer or a recent history thereof.

Severe coronary or cerebral arteriosclerosis with hypertension as well as serious cardiac arrhythmias are relative contraindications to parenteral treatment.

4.4 Special warnings and precautions for use

Since pentoxifylline is extensively metabolised 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 Trental therapy and may require lower doses.

Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension and arrhythmia. Controlled trials do not show that Trental causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible that some individuals will experience such responses. Careful monitoring is required in patients with acute arrhythmias or in patients with myocardial infarction.

Caution should be exercised and careful monitoring undertaken when administering Trental to patients with low or labile blood pressure, for example patients with severe coronary heart disease or relevant stenoses of blood vessels supplying the brain. In such patients any dose increase should be done gradually.

Hypersensitivity reactions, such as pruritus, rashes and urticaria do occur but progression to anaphylactoid shock and angioedema are rare. At the first signs of an anaphylactic/anaphylactoid reaction, Trental must be discontinued, and a physician must be informed.

Careful monitoring and adjustment (see section 4.2) are necessary in patients with impaired renal function (creatinine clearance below 30 mL/min).

Trental may exacerbate bleeding; careful patient selection and monitoring of at risk patients via haematocrit and/or haemoglobin determinations are recommended.

Particular careful monitoring is required in patients treated concomitantly with anti-vitamin K, platelet aggregation inhibitors, antidiabetic agents or ciprofloxacin.

Paediatric Use

Safety and effectiveness in children below the age of 18 years has not been established.

Elderly Use

Trental 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.

Effects on Laboratory tests

Urinary assays for pregnanediol may show false positive results in the presence of pentoxifylline and its metabolites.

4.5 Interaction with other medicines and other forms of interaction

There have been reports of bleeding (eg. skin, mucosa, gastrointestinal tract) and/or prolonged prothrombin time in patients treated with Trental with and, rarely without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients without risk factors complicated by haemorrhage (eg. recent surgery, peptic ulceration) should have periodic examinations for bleeding including haematocrit and/or haemoglobin.

Trental has been used concurrently with digitalis and antiarrhythmics without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental. Periodic systemic blood pressure monitoring is recommended for patients receiving Trental concomitantly with antihypertensive

medicines, beta blockers, diuretics and other medicines with blood pressure lowering potential as their blood pressure lowering effects may be increased. If indicated, dosage of the antihypertensive agents should be reduced.

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

Trental should not be given concomitantly with ketorolac as there is increased risk of bleeding and/or prolongation of prothrombin time.

An increase in the level of theophylline and therefore an increase in the intensity and frequency of adverse events associated with theophylline may result from concomitant use with Trental.

Concomitant administration with ciprofloxacin may increase the serum concentration of pentoxifylline in some patients. Therefore, there may be an increase in and intensification of adverse effects associated with co-administration.

The blood sugar lowering effect of insulin or oral antidiabetics may be potentiated. In patients treated with hypoglycaemic agents, a moderate decrease in the dose of these agents may be required when Trental is prescribed. Patients undergoing such therapy should be monitored closely.

Post-marketing cases of increased anti-coagulant activity have been reported in patients concomitantly treated with pentoxifylline and anti-vitamin K. Monitoring of anti-coagulant activity in these patients is recommended when pentoxifylline is introduced or the dose is changed.

Potential additive effect with platelet aggregation inhibitors. Due to the increased risk of bleeding, the concomitant administration of a platelet aggregation inhibitor (such as clopidogrel, eptifibatide, tirofiban, epoprostenol, iloprost, abciximab, anagrelide, NSAIDs other than selective COX-2 inhibitors, acetylsalicylates (ASA/LAS), ticlopidine, dipyridamole) with pentoxifylline should be undertaken with caution.

Concomitant administration with cimetidine may increase the plasma concentration of pentoxifylline and the active Metabolite I.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1.

In teratogenic studies in rats and rabbits, oral doses of Trental up to 25 and 10 times the maximum recommended human daily dose caused no foetal malformation. Increased resorption was seen in rats at high doses. However, since no well-controlled studies in pregnant women have been carried out, Trental should not be used in pregnancy unless clearly needed.

Breast-feeding

Trental and its metabolites are excreted in human milk. A decision should therefore be made whether to discontinue breast-feeding or discontinue the medicine, taking into account the importance of the medicine to the mother.

Fertility

No effect known.

4.7 Effects on ability to drive and use machines

No effect known.

4.8 Undesirable effects

Clinical trials with Trental have been conducted in Australia, the United States and in Europe. The slow release formulation, Trental, was used in studies in Australia and Europe, while in the United States, studies were conducted using the capsule formulation, containing 200 mg pentoxifylline. In these studies, dosages used were 400 mg (tablets) two to three times daily or 200 mg - 400 mg (capsules) three times daily. Treatment periods for studies with Trental ranged up to 60 weeks. The following adverse effects have been reported in clinical trials or post-marketing.

Gastrointestinal

The most frequent (greater than 1% incidence) types of side effects seen with Trental (all formulations) were gastrointestinal upsets, including nausea, dyspepsia, vomiting, belching/flatus/bloating, abdominal pain, epigastric discomfort and diarrhoea. However, the controlled release preparation of Trental resulted in much fewer gastrointestinal side effects, the most common being dyspepsia 2.8% (placebo 4.7%), nausea 2.2% (placebo 0.8%), vomiting 1.2% and belching/flatus/bloating (0.6%). Anorexia, cholecystitis, constipation and a dry mouth/thirst have been reported with a frequency of less than 1%.

Central Nervous System

Side effects related to C.N.S. disturbances with an incidence of greater than 1% included dizziness, headache, insomnia and sleep disturbances and disorders, blurred vision, agitation/nervousness, drowsiness and tremor. Of these, the following were reported for the controlled release preparation Trental: dizziness 1.9% (placebo 3.1%), headache 1.2% (placebo 1.6%) and tremor 0.3% (placebo 0.8%). Anxiety and confusion have been reported with a frequency of less than 1%. Isolated cases of aseptic meningitis have been reported.

Cardiovascular

Only angina/chest pain was reported for Trental tablets, with an incidence of 0.3%, while for the capsule formulation flushing and arrhythmia/palpitation/tachycardia were also reported, with an incidence of greater than 1%. Reports of hypotension were rare (<0.1%). Dyspnoea and oedema have been reported with a frequency of less than 1%. Haemorrhage has also been reported (frequency unknown).

Hepatic

Isolated cases of intrahepatic cholestasis and jaundice as well as hepatitis and transaminase elevation have been reported.

Haemic and Lymphatic

Decreased fibrinogen, pancytopenia, purpura, aplastic anaemia, neutropenia and leukopenia. Isolated cases of thrombocytopenia have been noted.

Respiratory

Epistaxis, flu-like symptoms, laryngitis and nasal congestion have been reported rarely.

Hypersensitivity

Anaphylactic and anaphylactoid reactions have been reported. Pruritus, rashes and urticaria may occur with a frequency of 0.1% to 1% but progression to anaphylactoid shock (angioedema, bronchospasm) occurs only in isolated cases. Erythema (reddening of the skin) has been reported at an unknown frequency.

Miscellaneous

Rarely, the following were reported: brittle fingernails, blurred vision, conjunctivitis, earache, scotoma, bad taste in the mouth, excessive salivation, malaise, sore throat, swollen neck glands, weight change.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

Symptoms appear to be dose related. A report from a poison control centre on 44 patients taking overdoses of enteric coated pentoxifylline tablets noted that symptoms 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.

Initial symptoms of acute overdose with pentoxifylline may be nausea, dizziness, tachycardia or a fall in blood pressure. Signs such as fever, agitation, flushing, loss of consciousness, areflexia, tonic-clonic convulsions and coffee-ground vomiting (indicating gastrointestinal bleeding) may occur.

Treatment

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

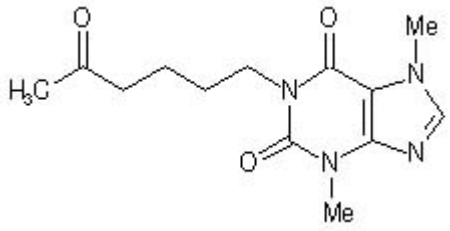
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripheral vasodilators, ATC code: C04AD03

Chemical Structure:



$C_{13}H_{18}N_4O_3$ 278.3102

CAS Number: 6493-05-6

A trisubstituted xanthine derivative designated chemically as 1-(5-oxohexyl)-3, 7-dimethylxanthine, IUPAC name: 3,7-dimethyl-1-(5-oxohexyl)-3.7-dihydro-1H-purine-2,6-dione. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene.

Site and Mode of Action

It is thought that pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. Some of the mechanisms by which this is thought to occur include dose-related haemorrheological effects, such as decreased blood viscosity, increases impaired erythrocyte deformability, decreased plasma fibrinogen and enhanced platelet deaggregation. However the precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be clearly defined.

5.2 Pharmacokinetic properties

After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing.

Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxy-hexyl]-3,7-dimethylxanthine) and Metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than of pentoxifylline. Following oral administration of aqueous solutions containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (cytochrome P450) following multiple oral doses.

Excretion is almost totally urinary: the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in faeces. Food intake shortly before dosing delays absorption of an immediate release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of Trental have not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years). After administration of the 400 mg controlled-release Trental tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over an extended period of time. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

5.3 Preclinical safety data

Nothing of clinical relevance.

Carcinogenicity

Long-term (18 month) studies to determine any carcinogenic potential of pentoxifylline have been conducted in mice and rats. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group. The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumour that is common in aged rats.

Genotoxicity

Pentoxifylline was devoid of mutagenic activity in various strains of Salmonella (Ames test) when tested in the presence and absence of metabolic activation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hyetellose

Povidone

Purified talc

Magnesium stearate

Hypromellose

Titanium dioxide

Erythrosine

Macrogol 8000

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

PVC/Al blister packs of 50 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

New Zealand

Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

22 June 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Update to fonts and styles throughout data sheet.
8	Change of sponsor