Trental 400 Prescribing Information

1. NAME OF THE MEDICINAL PRODUCTS

Trental 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pentoxifyilline 400mg
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the improvement of blood flow in the peripheral blood vessels.

4.2 Posology and method of administration

Chronic peripheral arterial occlusive disease at Fontaine stage IIb (intermittent claudication)
Unless otherwise prescribed, 1 Trental 400 mg prolonged-release tablet three times daily (equivalent to 1,200 mg pentoxifylline per day).

Special dosage instructions may be necessary for patients with low or fluctuating blood pressure levels.

In patients with impaired renal function (creatinine clearance less than 30 ml/min), the dose should be titrated to 50–70% of the standard dose, depending on individual tolerability, e.g. by taking 400 mg pentoxifylline twice daily instead of 400 mg pentoxifylline three times a day.

In the case of patients with severe hepatic dysfunction, a dose reduction is required, which should be decided by the doctor on an individual basis according to the severity of the illness and tolerability.

Inner ear dysfunction caused by circulatory disorders (including hardness of hearing, sudden hearing loss).
Unless otherwise prescribed, 1 Trental 400 mg prolonged-release tablet twice daily or three times a day (equivalent to 800–1,200 mg pentoxifylline per day).

In cases of severe circulatory disturbances, a combination with parenterally administered Trental 100 mg or 300 mg ampoules (IV infusion) can accelerate the onset of action
The total daily dose (parenteral + oral) should essentially not exceed 1,200 mg pentoxifylline.
Depending on the severity of symptoms, oral-only treatment, combined oral-parenteral treatment (IV infusion) or parenteral-only treatment (IV infusion) can be administered.

Method and duration of administration
The prolonged-release tablets should be swallowed whole (without chewing) with plenty of liquid following a meal. Duration of use must be tailored to the individual clinical condition and is decided by the doctor.

Note:
In the case of accelerated gastro-intestinal passage (laxatives, diarrhoea, surgical shortening of the intestine), elimination of tablet residues can occur in isolated cases. If premature elimination occurs only now and again, no importance need be attributed to the process.

4.3 Contraindications

Trental 400 is contra-indicated in cases where there is known hypersensitivity to the active constituent, pentoxifylline other methyl xanthines or any of the excipients.

Also in patients with cerebral haemorrhage, or other clinically relevant bleeding (increased risk of haemorrhage), extensive retinal haemorrhage (increased risk of bleeding), acute myocardial infarction and severe cardiac arrhythmias, gastric and/or intestinal ulcers, bleeding diathesis.

If retinal hemorrhages occur during treatment with pentoxifylline, use of the medicinal product must be discontinued at once.

4.4 Special Warnings and precautions for use

At the first signs of an anaphylactic/anaphylactoid reaction, Trental 400 must be discontinued immediately, and a physician must be informed.

Particular careful monitoring is required:
In patients with cardiac arrhythmias, hypotension or severe coronary artery disease following a heart attack or postoperatively following surgical interventions, Trental 400 should be used with caution, as a transient hypotensive effect is possible and, in isolated cases, might result in a reduction in coronary artery perfusion.

In patients with systemic lupus erythematosus (SLE) or mixed connective tissue disease, pentoxifylline should only be used after careful assessment of the risks and benefits.

Due to the risk of aplastic anaemia during treatment with pentoxifylline, the blood count should be regularly monitored.

Particularly careful monitoring is required in patients with impaired renal function. In patients with a creatinine clearance of less than 30 ml/min it may be necessary to reduce the daily dose of Trental 400 to one or two tablets to avoid accumulation. In patients with severely impaired liver function the dosage may need to be reduced.

In patients treated concomitantly with pentoxifylline and anti-vitamin K or platelet aggregation inhibitors (see also section 4.5).

In patients treated concomitantly with pentoxifylline and antidiabetic agents (see also section 4.5).
In patients treated concomitantly with pentoxifylline and ciprofloxacin (see also section 4.5).

In patients treated concomitantly with pentoxifylline and theophylline (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

High doses of Trental injection have been shown, in rare cases, to intensify the hypoglycaemic action of insulin and oral hypoglycaemic agents. However, no effect on

insulin release has been observed with Trental following oral administration. It is recommended that patients under medication for diabetes mellitus be carefully monitored.

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.

Trental 400 may potentiate the effect of anti-hypertensive agents and the dosage of the latter may need to be reduced.

Trental 400 should not be given concomitantly with ketorolac as there is increased risk of bleeding and/or prolongation of prothrombin time.

Concomitant administration of pentoxifylline and theophylline may increase theophylline levels in some patients. Therefore there may be an increase in and intensification of adverse effects of theophylline.

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 reactions associated with co-administration.

Potential additive effect with platelet aggregation inhibitors:
Because of the increased risk of bleeding, the concomitant administration of a platelet aggregation inhibitor (such as clopidogrel, eptofibatine, tirofiban, epoprostenol, iloprost, abciximab, anagreline, NSAIDs other than selective COX-2 inhibitors, acetylsalicylates [ASA/LAS], ticlopidine, dipyrimadole) 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 Pregnancy and lactation

There is no information on the use of Trental in pregnancy but no untoward effects have been found in animal studies. Trental 400 should not be administered during pregnancy.

Pentoxifylline passes into breast milk in minute quantities. Because insufficient experience has been gained, the possible risks and benefits must be weighed before administration of Trental 400 to breast feeding mothers.

4.7 Effects on ability to drive and use machines

No effect known

4.8 Undesirable effects

These adverse reactions have been reported in clinical trials or post-marketing. Frequencies are unknown.

System Organ Class	Adverse Reaction
Investigations	Transaminases or alkaline phosphatases increased, Elevated blood pressure.

Cardiac disorders	Arrhythmia, Tachycardia, Angina Pectoris,
Blood and lymphatic system disorders	Thrombocytopenia with thrombocytopenia purpura and possibly fatal aplastic anaemia (pancytopenia), leukopenia/neutropenia
Nervous system disorders	Dizziness, Tremor, headache, Paresthesia, Convulsions, Intracranial bleeding, Meningitis aseptic*
Gastrointestinal disorders	Gastrointestinal disorder, Epigastric discomfort, Abdominal distension, Nausea, Vomiting, Bloatness, Diarrhoea, Constipation, Hypersalivation
Skin and subcutaneous tissue disorders	Pruritus, Erythema, Urticaria, Hot flush, Epidermal necrolysis, Stevens-Johnson syndrome, Sweating, Rash
Vascular disorders	Haemorrhage**, Hypotension
Immune system disorders	Anaphylactic reactions, Anaphylactoid reaction, Angioedema, Anaphylactic shock
Hepatobiliary disorders	Cholestasis
Psychiatric disorders	Agitation, Sleep disorder
Respiratory disorders	Bronchospasm, Dyspnoea
Eye disorders	Visual disturbances, Conjunctivitis, Retinal haemorrhage, Detachment of retina (If retinal haemorrhage occurs during treatment with pentoxifylline, the medicinal product must be discontinued immediately)
General dysorders	Fever, Peripheral oedema

Description of selected adverse reactions
* Reports of aseptic meningitis were predominantly in patients with autoimmune diseases (SLE, underlying connective tissue disorders)
** A few very rare events of bleeding (e.g. skin, mucosa) have been reported in patients treated with Trental with and without anticoagulants or platelet aggregation inhibitors. The serious cases are predominantly concentrated in the gastrointestinal, genitourinary, multiple site and surgical wound areas and are associated with bleeding risk factors. A causal relationship between Trental therapy and bleeding has not been established. Thrombocytopenia has occurred in isolated cases.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic @moh.gov.il).

4.9 Overdose

The treatment of overdosage should be symptomatic with particular attention to supporting the cardiovascular system.

Symptoms:
Dizziness, nausea, blood pressure decrease, tachycardia, flushing, loss of consciousness, fever, agitation, areflexia, tonic-clonic convulsions, coffee-ground vomit and arrhythmias.

Therapeutic measures:

If the overdose has happened recently, gastric lavage can be performed or further absorption can be delayed by the use of activated charcoal.

Treatment should be symptomatic since there is no known specific antidote. Observation under intensive care condition may be necessary to avoid complications.

Immediate measures in the event of severe hypersensitivity reactions (shock):
At the first signs (e.g. skin reactions such as urticaria, flushing, restlessness, headaches, outbreaks of sweating, nausea), establish a venous access. As well as the usual emergency measures, i.e. placing the patient in a supine position with the legs raised, keeping the airways clear and administering oxygen, immediate medication such as intravenous volume replacement, epinephrine (adrenaline) i.v., glucocorticoids (e.g. 250-1000 mg methylprednisolone i.v.) and histamine receptor antagonists is indicated.

Depending on the severity of the clinical symptoms, artificial respiration and, in the event of circulatory arrest, resuscitation in accordance with the usual recommendations may be required.

5. PHARMCOLOGICAL PROPERTIES

5.1 Pharmacdynamic properties

The half life of absorption of Trental 400 is 4-6 hours. Pentoxifylline is extensively metabolised, mainly in the liver. Sixty percent of a single dose of Trental 400 is eliminated via the kidney over 24 hours.

5.3 Preclinical safety data
Nothing of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hydroxyethylcellulose, talc, hypromellose, povidone, titanium dioxide (E 171), magnesium stearate, macrogol 8000, erythrosine (E 127).

6.2 Special precautions for storage
Do not store above 25^0C. Store in the original package in order to protect from moisture.

7. MANUFACTURER

Sanofi S.P.A., Italy

8. LICENSE HOLDER

Sanofi-aventis Israel ltd.

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in February 2016 + updates that don't require the Ministry of Health approval were transferred in April 2015.