Trental 400 Prescribing Information

1. NAME OF THE MEDICINAL PRODUCTS

Trental 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pentoxifylline 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 must not be used in the following circumstances:
- hypersensitivity to the active substance pentoxifylline, other methylxanthines or to any of the excipients of Trental 400mg.
- acute myocardial infarction
- severe cardiac arrhythmias
- intracerebral haemorrhage or other clinically relevant bleeding (increased risk of haemorrhage)
- gastric and/or intestinal ulcers
- bleeding diathesis
- retinal hemorrhages (increased risk of bleeding)

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 a hypersensitivity reaction, the medicinal product must be discontinued immediately and the doctor informed.

Particularly close medical supervision is necessary in patients with cardiac arrhythmias, hypotension, coronary sclerosis, following a heart attack or postoperatively following surgical interventions.

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.
Owing to the risk of haemorrhage, close supervision and frequent checks of the coagulation parameters (INR) are required during concomitant use of pentoxifylline and oral anticoagulants (vitamin K antagonists) (see also section 4.5).

Patients receiving concomitant treatment with pentoxifylline and oral antidiabetics or insulin, must be carefully monitored (see also section 4.5).

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

Elimination of pentoxifylline may be delayed in patients with impaired renal function (creatinine clearance less than 30 ml/min) or severe hepatic dysfunction. Appropriate monitoring is required.

*Patients with impaired renal function:*
In patients with impaired renal function (creatinine clearance less than 30 ml/min), the dose should be adjusted 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.

*Patients with severe liver dysfunction:*
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.

### 4.5 Interaction with other medicinal products and other forms of interaction

The following interactions of this medicinal product must be taken into account:

**Antihypertensives:**
Pentoxifylline may increase the effect of antihypertensives or medications with a hypotensive potential: the decrease in blood pressure may be intensified

**Anticoagulants:**
Pentoxifylline may increase the effect of anticoagulants. In patients with increased bleeding tendency due to concomitant use of anticoagulant medications, any bleeding that occurs may be increased. Furthermore, cases of increased anticoagulation have been reported in patients receiving concomitant treatment with pentoxifylline and vitamin K antagonists (coumarins). Therefore, careful monitoring of the anticoagulant effect is recommended in such patients (e.g. by regular checks on INR), especially when therapy with pentoxifylline is initiated or the dosage changed.

**Oral antidiabetic drugs, insulin:**
There may be a more pronounced decrease in blood sugar, causing hypoglycemic reactions. Glycaemic control should be monitored at intervals determined on a case-by-case basis.

**Theophylline:**
Raised blood levels of theophylline are possible, so that undesirable effects of theophylline may be exacerbated during treatment of respiratory diseases.
Cimetidine:
Raised plasma levels of pentoxifylline and an increased effect of Trental 400mg are possible.

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

4.6 Pregnancy and lactation

Pentoxifylline should not be taken during pregnancy because there has been insufficient experience of its use in pregnant women (see also section 5.3).

During lactation, pentoxifylline passes into breast milk. However, the infant receives only minute amounts of the active substance. Therefore the indicated use of pentoxifylline during lactation is unlikely to have any effect on the infant. Prior to administering pentoxifylline in breast-feeding women, a careful benefit-risk assessment by the doctor is required.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and operate machinery have been observed.

4.8 Undesirable effects

The following undesirable effects, which have been reported in clinical studies or during post-marketing, can occur during treatment with Trental 400 mg.

The following categories are used for stating the frequency of undesirable effects:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Very rare: thrombocytopenia with thrombocytopenic purpura and possibly fatal aplastic anaemia (pancytopenia).
For this reason, the blood picture should be regularly monitored.

Immune system disorders
Uncommon: cutaneous hypersensitivity reactions (see Undesirable effects of the skin).
Very rare: severe anaphylactic or anaphylactoid reactions developing within minutes of pentoxifylline administration, such as angioedema, bronchospasm, anaphylactic shock.
At the first signs of a hypersensitivity reaction, the medicinal product must be discontinued immediately and the doctor informed.

**Psychiatric disorders**
Uncommon: agitation, sleep disturbances.

**Nervous system disorders**
Uncommon: dizziness, tremor, headache.
Very rare: paraesthesia, convulsions, intracranial bleeding. Symptoms of aseptic meningitis: patients with autoimmune diseases (SLE, mixed connective tissue disease) appear to be prone to these symptoms. In all observed cases, the symptoms were reversible upon discontinuation of pentoxifylline.

**Eye disorders**
Uncommon: visual disturbances, conjunctivitis.
Very rare: retinal haemorrhage, detachment of the retina.
If retinal haemorrhage occurs during treatment with pentoxifylline, the medicinal product must be discontinued immediately.

**Cardiac disorders**
Uncommon: cardiac arrhythmia, e.g. tachycardia.
Rare: angina pectoris, dyspnoea.

**Vascular disorders**
Common: flushing.
Rare: bleeding (see undesirable effects on various organs).

**Gastrointestinal disorders**
Common: gastrointestinal complaints, such as nausea, vomiting, bloatedness, pressure in the stomach, diarrhoea.
Rare: gastric and intestinal bleeding.

**Hepatobiliary disorders**
Very rare: intrahepatic cholestasis, elevation of liver enzymes (see Investigations).

**Skin and subcutaneous tissue disorders**
Uncommon: pruritus, erythema, urticaria.
Rare: mucocutaneous bleeding.
Very rare: epidermal necrolysis, Stevens-Johnson syndrome, sweating.

**Renal and urinary disorders**
Rare: urogenital bleeding.

**Investigations**
Rare: decreased blood pressure.
Very rare: increase in transaminases or alkaline phosphatases, elevated blood pressure.

**General disorders**
Uncommon: fever.
Rare: peripheral oedema.

4.9 Overdose

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. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Methylxanthine derivative with circulation-stimulating properties; haemorheological agent.

ATC code: C04AD03

Pentoxifylline improves the flow properties of the blood by lowering the elevated blood viscosity and possesses further pharmacological properties which are explained by the fact that it:

- increases impaired red cell deformability by inhibiting phosphodiesterase with a subsequent increase in intracellular cAMP and ATP and by inhibiting red cell aggregation
- inhibits platelet aggregation
- lowers pathologically raised plasma fibrinogen levels
- inhibits leucocyte activation and the adhesion of leucocytes to the vascular endothelium.

Studies investigating the effect of pentoxifylline on cardio- and cerebrovascular morbidity and/or mortality are not available.

5.2 Pharmacokinetic properties
Pentoxifylline undergoes prolonged release from Trental 400 mg over 10-12 hours so that constant blood levels are maintained during this period. The released pentoxifylline is rapidly and almost completely absorbed. The substance undergoes a marked first-pass effect so that the systemic availability is only 20-30%.

Pentoxifylline is metabolised almost entirely in the liver. The active main metabolite 1-(5-hydroxyhexyl)-3,7-dimethylxanthine (metabolite I) is measurable in plasma at a concentration twice that of the parent substance, with which it is in reversible biochemical equilibrium. Pentoxifylline and metabolite I are therefore regarded as the active unit. Pentoxifylline undergoes biphasic elimination; the initial half-life of the parent substance is 0.4 - 0.8 h, that of the metabolites 1.0 - 1.6 h. The terminal plasma half-life of pentoxifylline is given as approx. 1.6 hours.

Elimination is largely renal in the form of water-soluble polar metabolites without conjugation; only 4% is eliminated with the faeces. Unchanged pentoxifylline is only excreted in traces.

Metabolite excretion is delayed in patients with severely impaired renal function.

In patients with severe renal or hepatic dysfunction, the elimination half-life is prolonged and absolute bioavailability is increased (see sections 4.2 and 4.4).

5.3 Preclinical safety data
In human subjects, oral doses of 80 mg/kg body weight produced the signs of overdosage listed in section 4.9. (q.v.).

In chronic toxicity studies, no substance-related toxic organ damage was detected after feeding with pentoxifylline for one year at doses of up to 1000 mg/kg BW daily in rats and up to 100 mg/kg BW daily in dogs. Lack of coordination, circulatory failure, haemorrhages, pulmonary oedema and giant cells in the testes were determined in isolated dogs receiving daily dosages of 320 mg/kg BW or above for one year.

Mutagenicity studies with pentoxifylline revealed no relevant evidence of mutagenic effects. The results of long-term studies of carcinogenic potential in mice and rats were negative.

Reproduction toxicity studies were performed on rats, mice, rabbits and dogs. There was no evidence of any teratogenic damage, embryotoxicity or effect on fertility. An increased absorption rate was observed with very high doses.

Pentoxifylline and its metabolites pass into breast milk.
6. PHARMACEUTICAL PARTICULARS

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

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

7. MANUFACTURER
Sanofi-Aventis S.P.A., Italy

8. LICENSE HOLDER
Sanofi-aventis Israel ltd.