SANOFI AVENTIS

Trental® 100 mg ampoules
Trental® 300 mg ampoules

1. NAME OF THE MEDICINAL PRODUCTS

Trental® 100 mg ampoules
Concentrate for solution for infusion

Trental® 300 mg ampoules
Concentrate for solution for infusion

Active substance: pentoxifylline

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trental 100 mg ampoules:
Each 5 ml ampoule contains 100 mg pentoxifylline.

Trental 300 mg ampoules:
Each 15 ml ampoule contains 300 mg pentoxifylline.

Excipient with known effect:
Contains sodium chloride (see section 4.4).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Initiation and support of oral treatment with pentoxifylline in peripheral arterial occlusive disease in Fontaine stage II (claudicatio intermittens).

Disturbances of inner ear function (impaired hearing, sudden loss of hearing, etc.) of circulatory origin.

4.2 Posology and method of administration

Oral treatment alone, combined oral and parenteral (IV infusion) or parenteral medication alone (IV infusion) may be carried out, depending on the severity of the clinical picture.

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

In patients with impaired renal function (creatinine clearance below 30 ml/min) the dose has to be adjusted to 50-70% of the standard dose depending on individual tolerability.

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.

Trental 100 mg ampoules and Trental 300 mg ampoules should be administered by intravenous infusion. The specified infusion time must be observed.

For patients with hypotension or circulatory instability, the infusion treatment should be started at a low dose and gradually increased because in these cases all blood flow-promoting medicines can give rise to a transient fall in blood pressure with a tendency to collapse and, very occasionally, anginal symptoms.

Suitable treatment must be given to patients suffering from heart failure. Large volumes of fluid should be avoided during infusion treatment of these patients.

The following dosage guidelines apply:

Peripheral arterial occlusive disease in Fontaine stage II (claudicatio intermittens)

The IV infusion treatment can be given according to the following regimen, depending on the severity of the circulatory disorder, body weight and tolerability:
An infusion of 100–300 mg pentoxifylline in a suitable vehicle solution once or twice daily.

The infusion time is 60 minutes/100 mg pentoxifylline.

The amount of pentoxifylline given by intravenous infusion should be supplemented by oral treatment with modified-release tablets containing 400 mg or 600 mg active substance. The total daily dosage (parenteral + oral) should not exceed 1,200 mg pentoxifylline.

Disturbances of inner ear function (impaired hearing, sudden loss of hearing, etc.) of circulatory origin.

For in-patient treatment with pentoxifylline intravenous infusion of 15 ml twice daily (2 x 300 mg pentoxifylline) over a period of 3 hours each is recommended. In addition, oral administration of pentoxifylline up to the maximum dose of 1,200 mg pentoxifylline per day is possible.

For outpatient treatment intravenous infusion of 15 ml once daily (1 x 300 mg pentoxifylline) over a period of 3 hours is recommended. For a short infusion 5 ml once daily (1 x 100 mg pentoxifylline) can be administered (duration of infusion: 60 minutes). Oral pentoxifylline up to the maximum dose of 1,200 mg pentoxifylline per day should be given in addition in each case.

In the context of a rheological strategy, haemodilution therapy with a suitable infusion solution (e.g. HAES) can be carried out in addition. For treating sudden loss of hearing, combinations of medicinal products may be indicated. In this case, the compatibility and possible interactions of the substances should be taken into account.

Children and adolscents
No experience is available concerning the use of Trental in children and adolescents

Physiological saline or other conventional solutions can be used as vehicles for the infusion treatment. Compatibility with the vehicle solution to be used should be tested in each individual case.

Follow-up treatment:

Once an improvement has been noted, the treatment can be continued with oral medication alone.

The duration of use must be tailored to the individual clinical condition and decided by the doctor.

4.3 Contraindications

Trental 100 mg and 300 mg ampoules must not be used in the following cases:
- hypersensitivity to pentoxifylline, other methylxanthines or to any of the other excipients listed in section 6.1,
- acute myocardial infarction,
- intracerebral bleeding or other clinically relevant bleeding (increased risk of haemorrhage),
- gastric and/or intestinal ulcers,
- bleeding diathesis,
- retinal haemorrhages (increased risk of bleeding).

If retinal haemorrhages occur under 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.

Parenteral administration of pentoxifylline requires particularly careful medical supervision in patients who would be at particular risk from a drop in blood pressure, e.g. patients

with severe coronary heart disease or relevant cerebrovascular stenosis.

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

For patients with hypotension or circulatory instability, the infusion treatment should be started at a low dose and gradually increased because in these cases all blood flow-promoting medicines can give rise to a transient fall in blood pressure with a tendency to collapse and, very occasionally, anginal symptoms.

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 picture should be regularly monitored.

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

Patients with impaired renal function
In patients with impaired renal function (creatinine clearance below 30 ml/min) the dose has to be adjusted to 50-70% of the standard dose depending on individual tolerability.

Patients with severe impairment of liver function
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.

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), stop the infusion, leave the IV line in place or gain 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 substitution, epinephrine (adrenaline) IV, glucocorticoids (e.g. 250-1,000 mg methylprednisolone IV) 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.

Note on specific excipients
One Trental 300 mg ampoule contains 1.8 mmol (41.3 mg) sodium. This has to be taken into consideration by patients on a controlled sodium diet.
Trental 100 mg ampoules contain sodium, but less than 1 mmol (23 mg) sodium per ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions of these medicinal products must be taken into account:

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

Anticoagulants
Pentoxifylline may increase the effect of anticoagulants. In patients with an 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 a therapy with pentoxifylline is initiated or the dosage changed.

Oral antidiabetics, insulin
There may be a more pronounced decrease in blood sugar, causing hypoglycaemic 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 the treatment of respiratory diseases.

Cimetidine
Raised plasma levels of pentoxifylline and an increased effect of pentoxifylline are possible.

Ciprofloxacin
After concurrent administration of ciprofloxacin and pentoxifylline increased serum concentrations of pentoxifylline were observed.

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 the breast milk but the baby 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 100 mg and 300 mg ampoules. Some undesirable effects can be avoided by reducing the rate of infusion.

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.

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via the

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripheral vasodilators, purine derivatives..

ATC code: C04AD03

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

- increases the disturbed red cell deformability by inhibiting phosphodiesterase with consecutive increase in intracellular cAMP and ATP and by inhibiting red cell aggregation,
- inhibits platelet aggregation,
- lowers the abnormally raised plasma fibrinogen levels,
- inhibits leukocyte activation and the adhesion of leukocytes 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 is metabolized almost entirely in the liver. The active main metabolite 1-(5-hydroxyhexyl)-3,7-dimethylxanthine (metabolite I) is measurable in plasma in a concentration that is twice higher than the parent substance, with which it is in a reversible biochemical redox 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 hours, that of the metabolites 1.0 -1.6 hours. 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 % are eliminated with the feces. Unchanged pentoxifylline is only excreted in traces.

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

In patients with 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

Doses of 80 mg/kg body weight given orally produced the overdose symptoms listed under section 4.9. in human subjects (see also there).

Tissue tolerability after parenteral administration is good.

In chronic toxicity studies, no substance-related toxic organ damage was detected after feeding with pentoxifylline for one year with doses of up to 1,000 mg/kg BW daily in rats and up to 100 mg/kg BW daily in dogs. Lack of coordination, circulatory failure, haemorrhages, pulmonary edema 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 teratogenic damage, embryotoxicity or an influence on fertility. An increased absorption rate was observed with very high doses.

Pentoxifylline and its metabolites pass into breast milk.

Trental® 100 mg ampoules
Trental® 300 mg ampoules

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, water for injections.

6.2 Incompatibilities

None known to date (see also section 4.2.).

6.3 Shelf life

5 years.

Discard residues after opening.

6.4 Special precautions for storage

No special storage conditions are required for these medicinal products.

6.5 Nature and contents of container

Trental 100 mg ampoules:
Packs with
5 ampoules of 5 ml
Combination pack for IV infusion (5 Trental 100 mg ampoules of 5 ml + 5 glass bottles of 100 ml Ringer's solution for infusion)
Hospital pack with 20 ampoules of 5 ml

Trental 300 mg ampoules:
Pack with 10 ampoules of 15 ml
Hospital pack with 20 ampoules of 15 ml

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main

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Postfach 80 08 60
D-65908 Frankfurt am Main

Tel.: (01 80) 2 22 20 10*

Fax: (01 80) 2 22 20 11*

E-mail: medinfo.de@sanofi.com

8. MARKETING AUTHORISATION NUMBERS

Trental 100 mg ampoules and Trental 300 mg ampoules:

Reg. no. 10021

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

February 2014

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

These medicinal products are marketed in accordance with the interim statutory regulations. Testing by the authorities for pharmaceutical quality, efficacy and safety is still in progress.

Direct all enquiries to:
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SmPC Service
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D-10831 Berlin
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* 0.06 €/call