Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trental 400 mg Modified-Release, Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of pentoxifylline.
Excipients: Sucrose 141.88 mg.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified-release, coated tablet.
Oblong, pink tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Uses: Trental 400 is indicated in the management of peripheral vascular disease.

Trental has been shown to increase cerebral blood flow but this may not necessarily be accompanied by an improvement in clinical signs and symptoms.

4.2 Posology and method of administration

The recommended initial dose is 1 tablet (400mg) three times daily; two tablets daily may prove sufficient in some patients, particularly for maintenance therapy.

Elderly: No special dosage requirements.

Children: No experience is available concerning the use of pentoxifylline in children. Consequently Trental 400mg is not currently recommended for use in children.

Special Cases:

In patients with impairment of renal function (creatinine clearance below 30ml/min) a dose reduction by approx. 30% to 50% may be necessary – guided by individual tolerance, see section 4.4

A dose reduction-guided by individual tolerance- is necessary in patients with severely impaired liver function, see section 4.4.

Treatment must be started at low-dose levels in hypotensive patients or patients whose circulation is unstable as well as in patients, who would be at particular risk from a reduction in blood pressure (e.g. patients with severe coronary heart disease or relevant stenoses of blood vessels supplying the brain); in such cases, the dose must only be increased gradually, see section 4.4.

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 acute myocardial infarction or cerebrovascular accident.
In patients with massive bleeding (risk of increased bleeding).
In patients with extensive retinal bleeding (risk of increased bleeding).

4.4 Special warnings and precautions for use

At the first signs of an analphylactic/anaphylactoid reaction, Trental must be discontinued or the infusion halted immediately and a physician informed.

In patients with hypotension or severe coronary artery disease, 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.

Treatment must be started at low-dose levels in hypotensive patients or patients whose circulation is unstable as well as in patients, who would be at particular risk from a reduction in blood pressure (e.g. patients with severe coronary heart disease or relevant stenoses of blood vessels supplying the brain); in such cases, the dose must only be increased gradually, see section 4.2

Particularly careful monitoring is required in patients with impaired renal function.
In patients with impaired renal function (creatinine clearance below 30ml/min), it may be necessary to reduce the daily dose of Trental 400 to one or two tablets to avoid accumulation, see section 4.2. In patients with severely impaired liver function the dosage may need to be reduced, see section 4.2.

Particularly careful monitoring is also required:

- In patients with severe cardiac arrhythmias
- In patients with myocardial infarction
- In hypotensive patients
- In patients with increased bleeding tendency due to e.g. anticoagulant medication or coagulation disorders. Concerning bleeding see also section 4.3
- In patients treated concomitantly with pentoxifylline and vitamin K antagonists (see also section 4.5)
- In patients treated concomitantly with pentoxifylline and antidiabetic agents (see also section 4.5)

The blood-sugar lowering effect of insulin or oral antidiabetics may be potentiated. Therefore it is recommended that patients under medication for diabetes mellitus be carefully monitored.
Contains 141.88mg of sucrose per tablet. Patients with rare hereditary problems of fructose intolerance glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This should be taken into account in patients with diabetes mellitus please see 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. Therefore it is recommended that patients under medication for diabetes mellitus be carefully monitored.

The blood-pressure lowering effect of antihypertensive agents and other drugs with blood-pressure-lowering potential may be increased by Trental. Therefore it is recommended that patients under medication for diabetes mellitus be carefully monitored.

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

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

Particularly careful monitoring is required in patients on medication susceptible to increase bleeding such as anticoagulants and antiplatelets agregants such as aspirin .

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

4.6 Fertility, pregnancy and lactation

Insufficient experience has been gained concerning use in pregnancy. Therefore, it is recommended that Trental is not used during pregnancy.

Pentoxifylline passes into breast milk in minute quantities. Because insufficient experience has been gained, the physician must carefully weigh the possible risks and benefits before administering Trental in breast-feeding women.

4.7 Effects on ability to drive and use machines

No effects 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 increased (Transaminase elevation), Blood pressure decreased (Fall in blood pressure)
Cardiac disorders:	Arrhythmia (Cardiac arrhythmia), Tachycardia, Angina Pectoris
Blood and lymphatic system disorders:	Thrombocytopenia (Thrombopenia
Nervous system disorders :	Dizziness, headache, meningitis aseptic (Aseptic meningitis)
Gastrointestinal disorders:	Gastroinitestinal disorder (Gastrointestinal complaints), Epigastric discomfort (Gastric pressure), Abdominal distension (fullness), Nausea, Vomiting, Diarrhoea
Skin and substances tissue disorders :	Pruritus, Erythema (Reddening of the skin), Urticaria
Vascular disorders:	Hot Flush (Flushes), Haemorrhage (Bleedings)
Immune system disorders :	Anaphylactic reaction, Analphylactoid reaction, Angioedema (Angioneurotic edema), Bronchospasm, Anaphylactic shock (shock)
Hepatobiliary disorders:	Cholestatis (Intrahepatic cholestasis)
Psychiatric disorders:	Agitation, Sleep disorder (Sleep disturbances)

4.9 Overdose

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

Symptoms of overdose:
Initial symptoms of acute overdose with pentoxifylline may be nausea, dizziness, tachycardia or a fall in blood pressure. Furthermore, signs such as fever, agitation, flush, loss of consciousness, areflexia, tonic-clonic convulsions and - as a sign of gastrointestinal bleeding- coffee-ground vomiting may occur.

Treatment of overdose:
No specific antidote is known. If ingestion has only just taken place, attempts may be made to prevent further systemic absorption of the active ingredient by primary elimination of the toxin (e.g. gastric lavage) or by delaying its absorption (e.g. activated charcoal).

The treatment of acute overdose and the prevention of complications may necessitate general and specific intensive medical monitoring and therapeutic measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation.

Pentoxifylline increases impaired erythrocyte deformability, reduces erythrocyte aggregation, reduces platelet aggregation, lowers fibrinogen levels, reduces the adhesiveness of leucocytes to the endothelium, reduces leucocyte activation and resulting endothelial damage, and lowers blood viscosity.

Hence, pentoxifylline promotes microcirculatory perfusion by improving the fluidity of the blood and by exerting antithrombotic effects.

Peripheral resistance may be reduced slightly if pentoxifylline is administered in high doses or by rapid infusion. Pentoxifylline exerts a mild inotropic effect on the heart.

5.2 Pharmacokinetic 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.

After oral administration, absorption of pentoxifylline is rapid and almost complete.

After almost complete absorption, pentoxifylline undergoes a “first pass “metabolism. The absolute bioavailability of the parent compound is 19 ± 13%. 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, with which it is in reversible biochemical redox-equilibrium. For this reason pentoxifylline and metabolite I are to be regarded as an active unit, and the availability of active substance is therefore significantly greater.

The elimination half-life of pentoxifylline after oral or intravenous administration is approx. 1.6 hours.

Pentoxifylline is completely metabolized and more than 90% is eliminated via the renal route in the form of unconjugated water-soluble polar metabolites. Metabolite excretion is delayed in patients with severely impaired renal function.

In patients with impaired liver function the elimination half-life of pentoxifylline is prolonged and the absolute bioavailability is increased.

5.3 Preclinical safety data

Acute toxicity
Acute toxicity studies have shown LD_{50} values in mice of 195 mg/kg body weight after intravenous and 1385 mg/kg body weight after oral administration, respectively, and in rats of 230 mg/kg body weight after intravenous and 1770mg/kg bodyweight after oral administration, respectively. This means that toxicity of pentoxifylline is low.

Chronic toxicity
Chronic toxicity studies showed no substance-related toxic organ damage following administration of pentoxifylline over 1 year to rats in daily does of up to 1000 mg/kg body weight and to dogs in daily doses of up to 100 mg/kg body weight. In one study, following doses of 320mg/kg body weight or higher given to dogs over one year, several animals showed lack of co-ordination, circulatory failure, bleedings, pulmonary oedema or giant cells in the testes.

Mutagenicity
Mutagenicity testing (Ames test, micronucleus test, UDS test) has revealed no evidence of a mutagenic effect.

Carcinogenicity
In mice given oral doses of pentoxyifylline up to 450mg/kg body weight daily over 18 months, no indications of any carcinogenic effects were revealed.

In female rats receiving oral doses of pentoxifylline up to 450vmg/kg body weight daily over 18 months, an increased number of benign mammary fibroadenomas were observed. However, benign mammary fibroadenomas often occur spontaneously in older rats.

Reproduction toxicology
An increased number of intrauterine deaths were observed in rats given extremely high doses. Notwithstanding, reproduction studies in mice, rats, rabbits and dogs, overall yielded no evidence of teratogenicity, embryotoxicity, or of any impairment of fertility or perinatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hyetellose
Povidone
Talc
Magnesium stearate
Sucrose
Acacia
Macrogol 6000
Erythrosine (E127)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blister packs (Aluminium/PVC) containing 100 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 540/80/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 07 March 1977

Date of the last renewal: 07 March 2007

10 DATE OF REVISION OF THE TEXT

June 2010