

**IRISH MEDICINES BOARD ACT 1995**

**MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998**

**(S.I. No.142 of 1998)**

**PA0540/080/001**

Case No: 2030105

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**sanofi-aventis Ireland Limited**

**Citywest Business Campus, Dublin 24, Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Trental Concentrate for Solution for Infusion 300mg/15ml**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/11/2006** until **02/01/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Trental Concentrate for Solution for Infusion 300mg/15ml

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15ml ampoule contains 300mg pentoxifylline (equivalent to 20mg/ml).

Each ampoule also contains 41mg (1.8 mmol) sodium, as excipient.

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless, sterile aqueous solution.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Trental is indicated in the management of peripheral vascular disease and cerebrovascular insufficiency. 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

Route of Administration: Intravenous or Intraarterial.

###### Adults only:

Parenteral administration: Intravenous Infusion: It is recommended that an initial dose of 100 mg in 250-500 ml of fluid be infused intravenously over 90-180 minutes. This dose may be increased by 50 mg per day up to a maximum daily dosage of 400 mg. The infusion time must be at least 60 minutes per pentoxifylline. Depending on the concomitant diseases (e.g. congestive heart failure), it may be necessary to keep the infusion volume small. In such cases a controlled volume infusion pump may be suitable.

Trental is compatible with 0.9% sodium chloride, 5% laevulose or glucose infusion solutions and Ringer's solution.

In patients with marked impairment of renal function (creatinine clearance below 10 ml/min) it may be necessary to reduce the daily dose of Trental by approx. 30% to 50% to avoid accumulation.

A dose reduction is necessary in patients with severely impaired liver function.

###### Elderly:

No special dosage requirements.

###### Children:

Trental is not recommended for use in children.

### 4.3 Contraindications

Trental is contra-indicated in cases where there is known hypersensitivity to the active constituent, pentoxifylline or other methyl xanthines. Also in cerebral haemorrhage, extensive retinal haemorrhage and acute myocardial infarction.

### 4.4 Special warnings and precautions for use

Particularly careful monitoring is required in patients with severe cardiac arrhythmias, myocardial infarction, diabetes mellitus and patients with increased bleeding tendency.

In patients with hypotension or severe coronary artery disease, Trental 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.

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

As with other compounds which inhibit cyclic AMP breakdown, Trental Injection can potentially increase the release of insulin from the pancreas, thereby enhancing the hypoglycaemic effect of antidiabetic agents. On rare occasions it may be necessary to reduce the insulin dosage in diabetic patients. However, this is unlikely to occur with normal therapeutic doses.

Trental may potentiate the effect of antihypertensive agents and the dosage of the latter may need to be reduced.

Concomitant administration of Trental and theophylline may increase theophylline levels in some patients.

Trental 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

Use in pregnancy is contraindicated. Pentoxifylline should not be used in women breast feeding infants.

### 4.7 Effects on ability to drive and use machines

Not applicable.

### 4.8 Undesirable effects

Gastrointestinal side effects (e.g. nausea, vomiting, diarrhoea) may occur, which in individual cases, could necessitate discontinuation of the treatment. Headache, dizziness, agitation and sleep disorders may occasionally occur, as well as, in isolated cases, intrahepatic cholestasis, transaminase elevation and aseptic meningitis.

There have been very rare reports of flushing, occasionally tachycardia and rarely angina pectoris and hypotension, particularly if using high doses of pentoxifylline. In such cases a discontinuation of the medication or a reduction of the daily dosage is required.

Hypersensitivity reactions such as pruritus, rash, urticaria anaphylactic or anaphylactoid reactions with angioneurotic oedema or bronchospasm may occur in isolated cases and usually disappear rapidly after discontinuation of the drug treatment.

A few very rare events of bleeding (e.g. skin, mucosa, gastrointestinal tract) 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 occurred in a few cases.

## 4.9 Overdose

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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 positive inotropic effect on the heart.

### 5.2 Pharmacokinetic properties

The elimination half-life of pentoxifylline after intravenous administration is approximately 1.6 hours.

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

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

### 5.3 Preclinical safety data

Nothing of clinical relevance.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride  
Water for injections

### 6.2 Incompatibilities

The medicinal product must not be mixed with other medical products except those listed in section 6.6.

### 6.3 Shelf Life

Unopened 3 years.  
Once opened, use immediately and discard any remaining contents.

### 6.4 Special precautions for storage

Do not store above 30°C.

## **6.5 Nature and contents of container**

Clear glass ampoules containing 15 ml of a clear, colourless sterile aqueous solution.

Boxes of 10 x 15ml ampoules.

## **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**

For single use only. Discard any unused contents.

Trental is compatible with 0.9% Sodium Chloride, 5% laevulose or glucose infusion solutions and Ringer's solution.

## **7 MARKETING AUTHORISATION HOLDER**

Sanofi-aventis Ireland Ltd.  
Citywest Business Campus  
Dublin 24

## **8 MARKETING AUTHORISATION NUMBER**

PA 540/80/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 03 January 1996

Date of last renewal: 03 January 2006

## **10 DATE OF REVISION OF THE TEXT**

Niovenber 2006