

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRENTILIN® Ampoule 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each ampoule contains 100 mg Pentoxifylline.

Excipient(s):

Sodium monohydrogen phosphate (6.90 mg)

Potassium dihydrogen phosphate (1.50 mg)

Sodium Chloride (35.00 mg)

Hydrochloric acid q.s.

Water for injection q.s. (5.0 ml)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ampoule containing solution for injection.

Colorless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Peripheral arterial occlusive diseases and arteriovenous circulatory disorders resulting from arteriosclerotic or diabetic causes (such as intermittent claudication, resting pain)
- Trophic disorders (such as leg ulcers and gangrene).
- Cerebral circulatory disorders.
- Ocular circulatory disorders with degenerative vascular processes.

4.2 Posology and method of administration

Posology / frequency and time of administration

In principle, the dosage depends on the type and severity of the circulatory disorder and on the patient's drug tolerance. The dosage is usually as follows:

The infusion time of 100 mg pentoxifylline should be at least 60 minutes. This period is at least 180 minutes for 300 mg.

Peripheral arterial occlusive disease (PAOD) Stage II (intermittent claudication) and circulatory disturbances in the eye; as initial therapy or adjuvant to oral treatment: It is recommended to administer an infusion of 100-600 mg pentoxifylline once or twice a day.

It is recommended to administer the pentoxifylline infusion in a suitable infusion solution; it may be necessary to keep the infusion volume low due to co-existing disease (e.g.

congestive heart failure). Especially in such cases, a controlled volume infusion pump may be useful.

When low-dose infusion therapy is administered in combination with oral therapy, the recommended total daily dose is 1200 mg pentoxifylline (intravenous plus oral).

For maintenance treatment, treatment may be continued with oral pentoxifylline alone.

Peripheral arterial occlusive disease (PAOD) Stage III and IV: Pentoxifylline may be administered as a continuous intravenous infusion in a carrier solution of up to 1200 mg in 24 hours or as two infusions of 600 mg each during at least 6 hours.

Method of application:

TRENTILIN[®] should be given as an intravenous infusion after being diluted with an appropriate fluid.

Physiological saline, Ringer solution can be used as the infusion solution. Compatibility with the solution to be used should be tested before each case (see section 4.4). Only clear solutions should be infused.

Depending on the comorbid disease (such as congestive heart failure), it may be necessary to keep the amount of infusion low. Especially in such cases, it may be useful to use a volume controlled infusion pump.

Additional information on special populations

Renal failure:

In patients with renal failure (creatinine clearance < 30 ml/min) the dose should be reduced about 30-50% of the therapeutic dose. Dose adjustment depends on the patient's drug tolerance.

Hepatic failure:

In patients with severe liver dysfunction, dose reduction is required depending on personal tolerance.

Pediatric population:

No experience is available concerning the use of TRENTILIN[®] in children.

Elderly:

The dose of should be adjusted carefully in the elderly. Generally, the treatment should start with low dose; then be adjusted depending on the frequency of liver, kidney and cardiac function decline and the presence of other accompanying diseases or drugs used. The active metabolite is largely excreted by the kidneys and the risk of toxic reaction may increase in patients with renal dysfunction. Careful dosing should be done, as renal function may be reduced in elderly patients, and monitoring of renal function may be useful.

Other:

Treatment should be initiated with low doses, then the dose should be gradually increased in patients with low blood pressure or labile circulatory systems, at special risk that lower blood pressure (e.g., patients with severe coronary heart disease or obstruction of blood vessels that supply blood to the brain).

4.3 Contraindications

TRENTILIN® should not be used in following patients and conditions:

- Patients who are hypersensitive to pentoxifylline, other methylxanthines or to any of the excipients
- Cerebral hemorrhage
- Extensive retinal hemorrhage
- Acute myocardial infarction
- Severe cardiac arrhythmia
- Bleeding diathesis
- Gastric and / or intestinal ulcer

4.4 Special warnings and precautions for use

At the first signs of an anaphylactic/anaphylactoid reaction, TRENTILIN® must be discontinued and a physician must be informed.

The following patients need careful monitoring;

- Those with low blood pressure,
- Those with severe coronary artery disease,
- Those with renal dysfunction (creatinine clearance <30 ml / min)
- Those with severe liver dysfunction,
- Those with increased bleeding tendency due to coagulation disorders and anticoagulant treatment (see section 4.3 on bleeding)
- Patients using pentoxifylline and vitamin K antagonists or low molecular weight heparin in combination
- Patients using pentoxifylline and antidiabetic agents in combination
- Those at risk of decrease in blood pressure (e.g. patients with severe coronary heart disease or obstruction of blood vessels that supply blood to the brain)
- Those with systemic lupus erythematosus or mixed connective tissue disease
- The blood table should be monitored regularly due to the risk of aplastic anemia during treatment with pentoxifylline.
- TRENTILIN® contains less than 1 mmol (39 mg) of potassium (0.01 mmol) per ampoule; i.e. it is "potassium free".
- TRENTILIN® contains less than 1 mmol (23 mg) of sodium (0.72 mmol) per ampoule; i.e. it is "sodium free".

No experience is available concerning the use of TRENTILIN® in children.

4.5 Interaction with other medicinal products and other forms of interaction

Precaution is required in following cases:

The blood-sugar lowering effect of insulin or oral antidiabetic agents may be potentiated. Therefore it is recommended that patients under medication for diabetes mellitus be carefully monitored.

There have been post-marketing reports of increased anticoagulant activity in patients treated with pentoxifylline and vitamin K antagonists or low molecular weight heparin. Monitoring of anti-coagulant activity in these patients is recommended when pentoxifylline is introduced or the dose is changed.

Caution is required in following cases:

Blood pressure lowering effects of antihypertensive agents and the effects of drugs with blood pressure lowering potential may increase during TRENTILIN® treatment.

In some patients, concomitant use of pentoxifylline with theophylline may increase the level of theophylline. This may lead to increase or worsening of side effects associated with theophylline.

Concomitant use of cimetidine, ciprofloxacin and systemic ketorolac may increase the level/effect of pentoxifylline.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C

Women with childbearing potential / Contraception

No data available.

Pregnancy

There is no adequate experience with the use of pentoxifylline in pregnant women. Animal studies showed reproduction toxicity. Potential risk for human is unknown. TRENTILIN[®] should not be used in pregnancy unless required.

Lactation

Pentoxifylline passes into breast milk in small amounts. In the absence of adequate experience, TRENTILIN[®] should not be used in breastfeeding women without carefully considering potential risk and benefits.

Fertility

In rats exposed to very high doses, an increase in the number of intrauterine deaths was observed. However, no evidence of teratogenicity, embryotoxicity or fertility or perinatal developmental disturbance was found in reproductive research in mice, rats, rabbits and dogs.

4.7 Effects on ability to drive and use machines

There is no known side effect of TRENTILIN[®] on the ability to drive and use machines. Driving and using machines should be avoided in case of dizziness.

4.8 Undesirable effects

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1.000$ to $< 1/100$); Rare ($\geq 1/10.000$ to $< 1/1.000$); Very rare ($< 1/10.000$); Not known (cannot be estimated from the available data)

Following adverse reactions have been reported in clinical trials or post-marketing.

Blood and lymphatic system disorders

Very rare: Thrombocytopenic purpura with thrombocytopenia, aplastic anemia that may become fatal (pancytopenia)

Immune system disorders:

Uncommon: Hypersensitivity reactions of the skin

Very rare: Severe anaphylactic/anaphylactoid reaction with, for example, angioneurotic edema, bronchospasms, anaphylactic shock emerging within minutes following administration of pentoxifylline.

Psychiatric disorders:

Uncommon: Agitation, sleep disturbances

Nervous system disorders:

Uncommon: Dizziness, tremor, headache

Very rare: Paresthesia, convulsions, intracranial hemorrhage, aseptic meningitis symptoms
(In patients with autoimmune diseases such as SLE, mixed connective tissue disease)

Eye disorders:

Uncommon: Blurred vision, conjunctivitis

Very rare: Retinal hemorrhage, retinal detachment

Cardiac disorders:

Uncommon: Cardiac arrhythmia (tachycardia)

Rare: Angina pectoris dyspnea

Vascular disorders:

Common: Hot flushes with reddening of the face and neck

Rare: Hemorrhage

Gastrointestinal disorders:

Common: Gastrointestinal disturbances such as nausea, vomiting, flatulation, abdominal discomfort, diarrhea

Rare: Gastric and intestinal hemorrhage

Hepatobiliary disorders:

Very rare: Intrahepatic cholestasis, increased liver enzymes

Skin and subcutaneous tissue disorders: Uncommon: Itching, erythema, urticaria

Rare: Mucocutaneous bleeding

Very rare: Epidermal necrosis, Steven-Johnson syndrome, sweating

Renal and urinary disorders:

Rare: Urogenital bleeding

General disorders and administration site conditions

Uncommon: Fever

Rare: Peripheral edema

Investigations:

Rare: Decrease in blood pressure

Very rare: Increased transaminase levels, increase in blood pressure

Reporting of suspected adverse reactions

Reporting any suspected adverse reactions of drugs is very important after the authorization. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose

Signs:

Initial signs of acute overdose with pentoxifylline may be nausea, dizziness, tachycardia or decrease in blood pressure. Fever, agitation, flushing, loss of consciousness, areflexia, tonic-clonic convulsions and coffee-ground vomiting as a sign of gastrointestinal bleeding may also occur.

Treatment:

No specific antidote is known. If the overdose has yet to occur, attempts may be made to prevent further systemic absorption through primary elimination of the toxin (e.g., gastric lavage) or delaying absorption (e.g., activated charcoal).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Purine derivatives

ATC Code: C04AD03

Pentoxifylline increases erythrocyte deformability, reduces erythrocyte aggregation, reduces platelet aggregation, lowers fibrinogen levels, reduces endothelial adhesion of leukocytes, reduces leukocyte activation and endothelial damage, and reduces blood viscosity.

Thus, pentoxifylline increases microcirculation perfusion by increasing blood flow and antithrombotic effects.

If pentoxifylline is administered at high doses or with rapid infusion, peripheral resistance may decrease slightly. Pentoxifylline has a slight positive inotropic effect on the heart.

5.2 Pharmacokinetic properties

Absorption:

Since oral absorption of pentoxifylline is rapid and almost complete following oral administration, complete absorption is expected following intravenous administration.

Distribution:

Pentoxifylline undergoes “first-pass” metabolism following administration and absorption.

Biotransformation

The main biotransformation product is Metabolite V. The active parent metabolite, 1- (5-hydroxyhexyl) -3,7-dimethyl-xanthene (metabolite I), can be measured as twice the plasma concentration of the parent compound with reversible biochemical redox stabilization. For this reason, pentoxifylline and metabolite I should be considered as a single active unit and therefore the availability of the parent compound is significantly higher. Pentoxifylline is completely metabolized.

Elimination:

After intravenous administration, the elimination half-life of pentoxifylline is about 1.6 hours.

More than 90% of the non-conjugated water soluble polar metabolites are excreted via the kidney. The excretion is almost entirely with urine. Essentially no compounds are present in the urine. Although large changes in plasma levels of the parent compound and its metabolites can be seen, the amount of Metabolite V is stable and dose-proportional. Less than 4% of the administered dose is excreted in the feces.

Special Populations

Renal failure:

Metabolite excretion is delayed in patients with severe renal impairment.

Hepatic failure:

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

Elderly:

In elderly (60-68 years, n = 6), the AUC of pentoxifylline is increased and the elimination rate is reduced compared to the younger population (22-30 years, n = 6) (See Section 4.2. Elderly)

5.3 Preclinical safety data

Acute toxicity

Acute toxicity studies have shown that LD50 values are 195 mg / kg body weight and 1385 mg / kg body weight, respectively, after intravenous and oral administration in mice and 230 mg / kg body weight and 1770 mg / kg body weight, respectively, after intravenous and oral administration in rats. This shows that the toxicity of pentoxifylline is low.

Chronic toxicity

Chronic toxicity studies have shown that there is no substance-related organ damage following administration of pentoxifylline in rats at doses up to 1000 mg / kg body weight per day for 1 year and doses up to 100 mg / kg body weight per day for dogs. In one study, following the administration of 320 mg / kg body weight or higher doses to dogs for one year, lack of coordination, circulatory failure, hemorrhages, pulmonary edema or giant cells were observed in several animal.

Mutagenicity

The mutagenicity test (Ames test, micronucleus test, UDS test) did not reveal any evidence of mutagenic effect.

Carcinogenicity

No evidence of any carcinogenic effect was observed in mice receiving oral pentoxifylline doses of up to 450 mg / kg body weight for 18 months.

An increase in the number of benign breast fibroadenomas was observed in female rats dosed with oral pentoxifylline doses of up to 450 mg / kg body weight for 18 months. However, in older rats, benign breast fibroadenomas often occur spontaneously.

Reproductive toxicology

In rats exposed to very high doses, an increase in the number of intrauterine deaths was observed. However, in reproductive research in mice, rats, rabbits and dogs, no evidence of teratogenicity, embryotoxicity or fertility or perinatal developmental disturbance was detected.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

Sodium monohydrogen phosphate
Potassium Dihydrogen Phosphate
Sodium Chloride
Hydrochloric acid
Water for injection

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

36 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

Available in boxes of 5 ampoules.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”. There is no special requirement.

7. MARKETING AUTHORIZATION HOLDER

Santa Farma İlaç San. A.Ş.
Okmeydanı, Boruçiçeği Sok. No.: 16
34382 Şişli- İSTANBUL
0212 220 64 00
0212 222 57 59

8. MARKETING AUTHORIZATION NUMBER(S)

173/31

9. DATE OF FIRST MARKETING AUTHORIZATION/RENEWAL OF THE MARKETING AUTHORIZATION

Date of first marketing authorization: 12.04.1995

Date of renewal: 12.04.2010

10. DATE OF REVISION OF THE TEXT
