

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRENTILIN[®] retard 400 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Pentoxifylline 400 mg

Excipients:

Lactose Monohydrate of Bovine Origin 65.0 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

White, biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Occlusive diseases of the peripheral arteries and arteriovenous circulatory disorders caused by atherosclerotic or diabetic conditions (such as intermittent claudication, rest pain), as well as trophic disorders (such as leg ulcers and gangrene)

4.2 Posology and method of administration

Posology/application frequency and duration:

As a principle, the dosage is based on the type and severity of circulatory disorder, and on how the patient tolerates the drug. Generally the dosage is administered as follows:

Unless otherwise recommended by the physician, 1 tablet TRENTILIN[®] 400 is administered two or three times daily.

Method of Administration:

The tablets are swallowed without chewing with plenty of liquid (approximately ½ glass) with or immediately following a meal.

Additional information about special populations:

Renal impairment:

In patients with renal impairment (creatinine clearance below 30 ml/min), a dose reduction by approximately 30% to 50% may be necessary. Dose reduction depends on individual tolerance regarding patient.

Liver impairment:

In patients with severe renal impairment, the dosage may need to be reduced depending on individual tolerance.

Pediatric population:

There is no experience on the use of TRENTILIN® in children.

Geriatric population:

There are no specific considerations regarding the use in elderly patients.

In patients with low blood pressure or labile circulatory systems, and in those at particular risk due to blood pressure-lowering effects (e.g., patients with severe coronary heart disease or with occlusion of cerebral blood vessels), treatment should be initiated at a low dose and gradually increased.

In cases of accelerated gastrointestinal transit (due to the use of laxatives, diarrhea, or surgically shortened intestines), the excretion of undissolved film-coated tablet fragments may rarely occur. In such cases, consult your doctor.

4.3 Contraindications

- Patients with hypersensitivity to pentoxifylline, other methylxanthines, or any of the excipients (see section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION),
- Severe hemorrhages (as it may increase the risk of bleeding),
- Severe retinal hemorrhages (as it may increase the risk of bleeding).

4.4 Special warnings and precautions for use

Careful monitoring is required in the following patients;

- Patients with severe cardiac arrhythmias, as pentoxifylline may exacerbate arrhythmias.
- Recent myocardial infarction, due to the potential risk of early cardiac arrhythmias and hypotension.
- Hypotension, as further reductions in blood pressure may occur (see section 4.2 *Posology and method of administration*).
- Renal impairment (creatinine clearance below 30 mL/min), due to the risk of drug accumulation and increased adverse effects (see section 4.2).
- Severe hepatic impairment, because of the risk of drug accumulation and enhanced adverse reactions (see section 4.2).
- Coagulation disorders and conditions associated with increased bleeding tendency (e.g., anticoagulant therapy), as pentoxifylline may increase the risk of bleeding (see section 4.3 *Contraindications*).
- Patients at risk of hypotension, such as those with severe coronary artery disease or occlusion of cerebral arteries.

TRENTILIN® contains lactose monohydrate of bovine origin as an excipient. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

- The blood pressure-lowering effects of antihypertensive agents (e.g., ACE inhibitors) and drugs with hypotensive potential (e.g., nitrates) may be enhanced during treatment with TRENTILIN®.
- Pentoxifylline may enhance the blood glucose-lowering effects of insulin or oral antidiabetic agents, thereby increasing the risk of hypoglycemia. Patients receiving treatment for diabetes mellitus should be monitored carefully.
- Concomitant use of pentoxifylline and theophylline may increase the plasma concentration of theophylline in some patients, potentially leading to enhanced or aggravated theophylline-related adverse effects.

4.6 Pregnancy and lactation

General advice

Pregnancy category C.

Women with child bearing potential / Birth control (Contraception)

There is no data.

Pregnancy period

Since there is no experience on the use of pentoxifylline in pregnancy.

Lactation period

Pentoxifylline passes into breast milk in minute quantities. Because insufficient experience has been gained, the possible risks and benefits must be carefully weighed before administration of TRENTILIN® to breastfeeding mothers.

Reproduction / Fertility

It is not known whether treatment with TRENTILIN® affects human fertility.

4.7 Effects on ability to drive and use machines

No adverse effect of TRENTILIN® known on ability to drive and use machines.

4.8 Undesirable effects

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data)

Blood and lymphatic system disorders:

Very rare: Thrombocytopenic purpura and thrombocytopenia, aplastic anemia which can be fatal (pancytopenia).

Immune system disorders:

Uncommon: Skin hypersensitivity reactions

Very rare: Angioedema, bronchospasm and anaphylactic/anaphylactoid reactions like anaphylactic shock which is seen within minutes after administration of pentoxifylline

Psychiatric disorders:

Uncommon: Agitation, sleep disorders.

Nervous system disorders:

Rare: Dizziness, headache, agitation, sleep disturbances

Cardiac disorders:

Rare: Angina pectoris, dyspnea

Gastrointestinal disorders:

Especially when TRENTILIN® is taken at high doses, a feeling of heaviness or fullness in the stomach, nausea, vomiting, or diarrhea may occur.

Hepatobiliary disorders

Very rare: Intrahepatic cholestasis and elevation in liver enzymes

General disorders and disorders related to the administration site:

Especially when TRENTILIN® is taken at high doses, flushing (a sensation of heat accompanied by skin redness) may occur.

Reporting of suspected adverse reactions

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose and treatment**Symptoms:**

Initial symptoms of pentoxifylline overdose may include nausea, dizziness, tachycardia or hypotension. In addition, fever, agitation, flush, loss of consciousness, areflexia, tonic-clonic convulsions and –as a symptom of gastrointestinal bleeding- coffee-ground vomiting may be observed.

Treatment:

There is no known specific antidote. If over dosage is just recent, attempts may be done to prevent more systemic absorption by primary elimination of the toxin (e.g. gastric lavage) or retardation of the absorption (e.g. Activated charcoal). In addition to general measures to manage overdose, particular attention should be paid to monitoring blood pressure. If blood pressure drops significantly, a plasma substitution solution should be administered via infusion.

The airways must be kept clear, and if convulsions occur, diazepam should be administered.

5. PHARMACOLOGICAL PARTICULARS**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Purine derivatives

ATC code: C04AD03

Pentoxifylline increases altered red blood cell deformability, decreases erythrocyte aggregation, decreases thrombocyte aggregation, lowers fibrinogen levels, decreases adhesion of leucocytes to endothelium, lowers leucocyte activation and endothelium damage related to it and lowers blood viscosity.

Hemorheological effect

Pentoxifylline improves the decreased flexibility of erythrocytes, inhibits erythrocyte aggregation, reduces elevated fibrinogen levels, inhibits platelet aggregation, and improves blood flow properties by reducing increased blood viscosity.

Hemodynamic effect

It decreases peripheral resistance and increases cardiac output (positive inotropic effect).

5.2 Pharmacokinetic properties

Absorption and Distribution:

Pentoxifylline is rapidly absorbed from the gastrointestinal tract due to its good solubility in both water and lipids. Peak plasma concentrations are reached approximately 30 minutes after the active substance is released.

Biotransformation and Elimination:

The half-life of pentoxifylline is approximately 1 hour. Pentoxifylline is completely metabolized and more than 90% is excreted via the kidneys in the form of water-soluble, unconjugated polar metabolites. Due to its short half-life, accumulation of pentoxifylline is not expected. However, in cases of impaired renal function, the excretion of metabolites may be delayed.

5.3 Preclinical safety data

Long-term studies on the carcinogenic potential of pentoxifylline have been conducted in rats and mice at dietary doses of up to 450 mg/kg (equivalent to 19 times the recommended maximum daily dose). The drug was administered for a total of 18 months in both rats and mice. In the rat study, a statistically significant increase in benign mammary fibroadenomas was observed in females at the 450 mg/kg dose level. The relevance of this finding to humans is unknown. Pentoxifylline did not show mutagenic effects when tested in the presence or absence of metabolic activation in mammalian cell cultures (unscheduled DNA synthesis test), various strains of *Salmonella* (Ames test), or the in vivo mouse micronucleus test.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate (bovine-derived)

Copovidone (VA64)

Hypromellose (Hydroxypropyl methylcellulose)

Magnesium stearate

Titanium dioxide

Talc

Polyethylene glycol

Hypromellose E15 (Hydroxypropyl methylcellulose E15)

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

It is presented in blister packs containing 20 film-coated tablets.

6.6 Special Precautions for Disposal and Other Handling

Unused products or residual materials should be discarded according to “Medicinal waste control regulation” and “Control of Packaging materials and Packaging Residual Materials Regulation”.
No special requirements.

7. MARKETING AUTHORIZATION HOLDER

SANTA FARMA ILAC SAN. A.S. H. Edip Adivar / Boru Cicegi Sokak No: 16 Sisli, Istanbul, Türkiye

Tel: (+90 212) 220 64 00

Fax: (+90 212) 222 57 59

8. MARKETING AUTHORIZATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

[To be completed nationally]

10. DATE OF REVISION OF THE SPC

[To be completed nationally]