Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Thioctacid® 600 T
Solution for Injection, containing 600 mg thioctic acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Thioctic acid, Trometamol salt
24 ml of solution for injection contain 952.3 mg of thioctic acid, Trometamol salt (equivalent to 600 mg of thioctic acid)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms of peripheral (sensomotor) diabetic polyneuropathy

4.2 Posology and method of administration

In cases of symptoms of peripheral (sensomotor) diabetic polyneuropathy, for adults intravenous application of a daily dosage of 24 ml of solution for injection (equivalent to 600 mg of thioctic acid/day) is recommended.

During the initial phase of treatment, the injection solution shall be applied intravenously for a period of 2 to 4 weeks.

Intravenous application may be performed by injecting the undiluted solution by means of an injection syringe over a period of not less than 12 minutes.
After the contents of Thioctacid 600 T have been mixed with 100 – 250 mg of 0.9%-conc. Sodium chloride solution, the product can also be administered in form of a short-duration infusion over a period of not less than 12 minutes. Due to the fact that the active substance is sensitive to light, the short-duration infusion shall be prepared just shortly before its use. The infusion solution must be protected from light (e. g. by means of aluminium foil). When protected from light, the infusion solution has a shelf life of about 6 hours. Particular attention shall be paid to the fact that the **duration of infusion must not be less than 12 minutes.**

It is recommended to continue treatment by taking 300 mg to 600 mg of thioctic acid daily in form of oral pharmaceutical forms.

The basis for treatment of diabetic polyneuropathy is an optimum diabetic control.

Paediatric population

Thioctacid 600 T is contraindicated in children and adolescents (refer to section 4.3).

4.3 Contraindications

Thioctacid 600 T is absolutely contraindicated in patients with known hypersensitivity to thioctic acid or any of the other ingredients.

Caution:
Children and adolescents must not be treated with Thioctacid 600 T as there is no clinical experience with this age group.

4.4 Special warnings and precautions for use

In relation with parenteral application of Thioctacid 600 T, hypersensitivity reactions up to anaphylactic shock reactions were seen (refer to section 4.8). Therefore, patients must be monitored carefully. In case of the occurrence of early symptoms (such as itching, nausea, sickness etc.), treatment must be stopped immediately; if appropriate, further therapeutic measures must be taken.

Abnormal smelling of the urine can be noticed after administration of Thioctacid 600 T which has no clinical relevance.

Cases of Insulin Autoimmune Syndrome (IAS) have been reported during treatment with thioctic acid. Patients with human leukocyte antigen genotype such as HLA-DRB1*04:06 and HLA-DRB1*04:03 alleles, are more susceptible to develop IAS when treated with thioctic acid. HLA-DRB1*04:03 allele (susceptibility to IAS odds ratio: 1.6) is especially found in Caucasians, with a higher prevalence in southern than in northern Europe and HLA-DRB1*04:06 allele (susceptibility to IAS odds ratio: 56.6) is especially found in Japanese and Korean patients.

IAS should be considered in the differential diagnosis of spontaneous hypoglycaemia in patients using thioctic acid (see section 4.8).

4.5 Interactions with other medicinal products and other forms of interaction

Loss of response to Cisplatin in concomitant treatment with Thioctacid 600 T.

The blood-sugar reducing effect of insulin and/or oral anti-diabetic agents may be enhanced. Therefore - in particular when treatment with thioctic acid is initiated – fine-meshed monitoring of the blood-sugar values will be indicated. In order to avoid symptoms of hypoglycaemia, it may become necessary in individual cases to reduce the dose of insulin and/or of the oral anti-diabetic agent.

Caution:
Regular consumption of alcohol is an important risk factor for the development and the progression of neuropathic clinical pictures and may therefore also have a negative influence on the success of treatment with Thioctacid 600 T. For this reason, it is generally recommended for patients suffering from diabetic polyneuropathy to avoid the consumption of alcohol as far as possible. This shall also apply to treatment-free intervals.

4.6 Fertility, pregnancy and lactation

Fertility
Reproductive toxicology studies have not revealed any indication of effects on fertility.

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). During pregnancy, Thioctacid 600 T should be used only after careful weighing of the risk-benefit ratio.

Lactation
It is unknown whether thioctic acid/metabolites are excreted in human milk.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Thioctacid 600 T therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Thioctacid 600 T can have a negative impact on the ability to drive and use machines. If side effects as dizziness/vertigo or other central nervous disorders occur, activities which require increased attention e.g. participation in road traffic and using machines or dangerous tools should be avoided.

4.8 Undesirable effects

Evaluation of the side effects is based on the following frequency information:
Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1.000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
Very rare (< 1/10,000)
Not known (Frequency cannot be estimated from the available data).

Blood and lymphatic system disorders
Very rare: Thrombopathy

Immune system disorders
Not known: Allergic reactions such as skin rash, urticaria, eczema and itching; anaphylactic reactions
Frequency unknown: Insulin autoimmune syndrome (see section 4.4)

Metabolism and nutrition disorders
Very rare: Hypoglycaemia*

Nervous system disorders
Uncommon: Dysgeusia
Very rare: Seizure, headache*, vertigo*, hyperhidrosis*

Eye disorders
Very rare: Diplopia, vision disorders*

Gastrointestinal system disorders
Uncommon: Nausea, vomiting

Skin and subcutaneous tissue disorders
Very rare: Purpura

General disorders and administration site conditions
Very rare: Injection site reactions

After rapid intravenous injection, commonly pressure in the head and respiratory distress may occur which will remit spontaneously.

* Due to enhanced glucose utilization, the blood-sugar level may drop in very rare cases. In this relation, hypoglycaemic symptoms accompanied by dizziness, sweating, headache and blurred vision were described.

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 German authority:

Bundesinstitut fuer Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger Allee 3
D-53175 Bonn, Germany
Website: http://www.bfarm.de.

4.9 Overdose

In case of overdosing, nausea, vomiting and headache may occur.

After accidental or suicidal uptake of oral doses ranging between 10 and 40 g of thioctic acid in connection with consumption of alcohol, severe intoxication – partially with lethal outcome – was seen. The clinical picture of such intoxication may initially include psychomotor restlessness or confused consciousness, in the further course usually generalized seizure and lactate acidosis will be developed. Furthermore, hypoglycaemia, shock, rhabdomyolysis, haemolysis, disseminated intravascular clotting (DIC), bone-marrow depression and multiple organ dysfunction resulting from intoxication with high doses of thioctic acid were reported.

Therapeutic measures in case of intoxication:
Even suspected significant intoxication with Thioctacid (e. g. more than 10 tablets containing 600 mg in adults and more than 50 mg/kg of body weight in children) shall require immediate admission to a hospital and initiation of standard measures used to treat intoxication (e. g. induction of vomiting, gastric lavage, activated charcoal, etc.). Treatment of generalized seizure, lactate acidosis and all other life-threatening consequences of intoxication shall be based on the principles of modern intensive care and shall be carried out symptomatically. Presently, the benefits of haemodialysis, haemoperfusion or filtration methods in forced elimination of thioctic acid have not yet been demonstrated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various alimentary tract and metabolism products
Other nervous system drugs
ATC Code: A16AX01

Thioctic acid is a vitamin-like, however endogenous substance having a coenzyme function in oxidative decarboxylation of alpha-keto acids.

Hyperglycaemia which is caused by Diabetes mellitus leads to accumulation of glucose to the matrix proteins of the blood vessels and thus to the formation of so-called "Advanced Glycosylation End Products". This process results in a reduction of the endoneural blood flow and in endoneural hypoxia/ischemia associated with increased production of free oxygen radicals which on their part damage the peripheral nerve. Also, depletion of anti-oxidant agents (such as glutathione) was seen in the peripheral nerve.

In studies in rats, diabetes was induced by means of streptozotocin which then caused the biochemical processes described above. Thioctic acid interacted with these processes resulting in a decreased formation of Advanced Glycosylation End Products, improvement of endoneural blood flow, elevation of the physiologic level of anti-oxidants of glutathione and as anti-oxidant for free oxygen radicals in the diabetic nerve.
These effects seen in experiments support the theory that functionality of the peripheral nerves can be improved by the use of thioctic acid. This applies to sensoric disorders in diabetic polyneuropathy, manifesting themselves by dysaesthesia, paraesthesia such as burning sensation, pain, numbness and formication.

In addition to the clinical findings made so far with regard to symptomatic treatment of diabetic polyneuropathy with thioctic acid, the favourable effect of thioctic acid on the studied symptoms burning sensation, paraesthesia, numbness and pain was demonstrated in the course of a multi-centre, placebo-controlled trial conducted in 1995.

5.2 Pharmacokinetic properties

Thioctic acid is subject to a marked first-pass effect in the liver. With regard to systemic availability of thioctic acid, there is substantial interindividual variation. Thioctic acid is biotransformed by oxidation of the side chains and conjugation and it is eliminated mainly via the kidney.

Plasma half-time of thioctic acid in humans comes to about 25 minutes and total plasma clearance to 10 – 15 ml/min/kg. At the end of an infusion of 600 mg over 12 minutes, the plasma concentration comes to about 47 µg/ml. In animal experiments (rat, dog), radioactive labelling made it possible to demonstrate a mainly renal excretion in form of metabolites at a rate of 80 - 90%. In humans as well, only small quantities of the eliminated intact substance are found in the urine. Biotransformation mainly occurs by oxidative side-chain reduction (beta-oxidation) and/or by S-methylation of the relevant thiols.

In vitro, thioctic acid does react with metallic ion complexes (e. g. with Cisplatin). Thioctic acid enters into difficultly soluble complex combinations with sugar molecules.

5.3 Preclinical safety data

a) Acute and chronic toxicity

The toxicity profile is characterised by symptoms related to the vegetative nervous system as well as to the central nervous system.
After multiple applications, other target organs of toxic doses mainly include the liver and the kidney.

b) Mutagenic and carcinogenic potential

Studies with regard to a mutagenic potential did not reveal any indication for genetic or chromosomal mutation. Following oral application in rats, there was no indication of a carcinogenic potential of thioctic acid from a carcinogenicity study. A study with
regard to a tumour-promoting effect of thioctic acid in relation with the carcinogen N-Nitroso-dimethyl amine (NDEA) came to a negative result.

c) Reproductive toxicity

In the rat, thioctic acid has no influence on fertility and early embryonic development up to a studied oral dose of 68.1 mg/kg maximum. After intravenous injection in the rabbit, no teratogenic properties were observed up to the maternal-toxic dose range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol, Water for injection.

6.2 Incompatibilities

In vitro, thioctic acid does react with metallic ion complexes (e. g. with Cisplatin). Thioctic acid enters into difficultly soluble complex combinations with sugar molecules (e. g. laevulose solution). Thioctacid 600 T is incompatible with glucose solutions, Ringer's solution as well as with solutions known to react with SH groups and/or disulphide bridges.

As carrier solution for the infusion of Thioctacid 600 T, only physiological salt solution must be used.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a place protected from light at a temperature not higher than 30°C.
Store in a place inaccessible to children.

6.5 Nature and contents of container

Container
25-ml amber glass ampoules, hydrolytic class I, with colour ring coding;
packed in PS blisters containing 5 ampoules each, sealed with PS film, white, 500 µm

Pack sizes
Original pack of 5 ampoules (N1) containing 24 ml of solution for injection each.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MEDA Pharma GmbH & Co. KG
Benzstrasse 1
61352 Bad Homburg (Germany)
Phone: + 49 (06172) 888 01
Fax: + 49 (06172) 888 2740
Email: medinfo@medapharma.de

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

23.03.2023

11. REPORTING OF SUPSPECTED ADVERSE REACTIONS

Reporting of suspected adverse reactions after authorization of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medical product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at www.pharm.am