Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Thioctacid® 600 HR
Film-coated tablet contains 600 mg alpha-lipoic acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Alpha-lipoic acid

1 film-coated tablet contains 600 mg of alpha-lipoic acid.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms of peripheral (sensomotor) diabetic polyneuropathy

4.2 Posology and method of administration

The daily dose is 1 film-coated tablet of Thioctacid 600 HR (equivalent to 600 mg of alpha-lipoic acid), to be taken in form of a single dose about 30 minutes prior to the first meal.

In case of severe symptoms of peripheral (sensomotor) diabetic polyneuropathy, treatment can be started by means of an infusion therapy with alpha-lipoic acid.

Thioctacid 600 HR Film-coated tablets shall be taken unchewed and with an appropriate quantity of liquid on an empty stomach. The uptake of food at the same time may impair the resorption of alpha-lipoic acid. Therefore, it is very important – in particular in patients with prolonged gastric emptying time – that the tablet will be taken half an hour before breakfast.

Due to the fact that diabetic polyneuropathy is a chronic disease, long-term treatment may be required.
The basis for treatment of diabetic polyneuropathy is an optimum diabetic control.

Thioctacid 600 HR is contraindicated in children (refer to section 4.3).

4.3 Contraindications

Thioctacid 600 HR is absolutely contraindicated in patients with known hypersensitivity to alpha-lipoic acid or any of the other ingredients.

Caution:
Children and adolescents must not be treated with Thioctacid 600 HR as there is insufficient clinical experience with this age group.

4.4 Special warnings and precautions for use

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

4.5 Interactions with other medicinal products and other forms of interaction

Loss of response to Cisplatin in concomitant use with Thioctacid 600 HR.

Alpha-lipoic acid is a metal chelator and should therefore normally not be administered together with metal-containing products (e. g. iron preparations, magnesium preparations and milk products due to their calcium content). If the total daily dose of Thioctacid 600 HR is taken 30 minutes before breakfast, the iron and/or magnesium preparations can then be taken at lunchtime or in the evening.

The blood-sugar reducing effect of insulin and/or oral anti-diabetic agents may be enhanced. Therefore - in particular when treatment with alpha-lipoic 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 HR. 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 Pregnancy and lactation

It is one of the general principles of pharmacotherapy that any medicinal product is to be used during pregnancy and/or the lactation period only after careful weighing of the risk-benefit ratio. Therefore, it is recommended that pregnant and/or breast-feeding women shall undergo treatment with alpha-lipoic acid only after careful appraisal of the indication by their doctor, even though studies concerning reproductive toxicology have not revealed any indication of an impact on fertility or early embryonic development and moreover, no harmful effects on the foetus were seen.

There are no reports about a possible passage of alpha-lipoic acid into the breast milk.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Evaluation of the side effects is based on the following frequency information:
Very common (≥ 10 %)
Common (≥ 1 % - < 10 %)
Uncommon (≥ 0.1 % - < 1 %)
Rare (≥ 0.01 % - < 0.1 %)
Very rare (< 0.01 % or unknown)

Gastro-intestinal disorders
Common:
Nausea
In very rare cases, gastro-intestinal disorders (such as vomiting, pain in the stomach, pain in the intestine and diarrhoea) were reported.

Hypersensitivity reactions
In very rare cases, allergic reactions such as skin rash, urticaria and itching may occur.

Nervous system disorders
Common:
Dizziness
Very rare:
Change or disturbance of taste sensation

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

4.9 Overdose

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

After accidental or suicidal intake of oral doses ranging between 10 and 40 mg of alpha-lipoic 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 in consequence of intoxication with high doses of alpha-lipoic acid were reported.

Therapeutic measures in case of intoxication:

Even suspected significant intoxication with Thioctacid 600 HR (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 alpha-lipoic acid have not yet been demonstrated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary system and metabolism
ATC- Code: A16AX01

Alpha-lipoic 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. Alpha-lipoic 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 alpha-lipoic 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 alpha-lipoic acid, the favourable effect of alpha-lipoic 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

After oral application, alpha-lipoic acid is rapidly absorbed in humans. Based on a marked first-pass effect, absolute bioavailability (compared to i.v. application) of orally administered alpha-lipoic acid comes to about 20 %. Due to rapid distribution in the tissue, plasma half-time of alpha-lipoic acid in humans comes to about 25 minutes. Compared to drink solutions, relative bioavailability of alpha-lipoic acid after oral administration of solid pharmaceutical forms is higher than 60 %. Peak plasma levels of about 4 µg/ml are measured about 0.5 hours after oral administration of 600 mg of alpha-lipoic acid. 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, alpha-lipoic acid does react with metallic ion complexes (e. g. with Cisplatin). Alpha-lipoic acid enters into difficultly soluble complex combinations with sugar molecules.

A comparative bioavailability study (open-labelled, cross-over) conducted in 1997 in 24 healthy subjects (22 - 40 years of age) did result after administration of a single dose of one film-coated tablet of Thioctacid 600 HR compared to a drink solution (equivalent to 600 mg alpha-lipoic acid each) in the following values for the enantiomers of alpha-lipoic acid:

	Study product		Reference	
	R-α-Lipoic acid	S-α-Lipoic acid	R-α-Lipoic acid	S-α-Lipoic acid
C_{max} [ng/ml]	2796.96	1282.57	8946.44	4201.41
VK (%)	60.59	54.04	44.90	44.50
t_{max} [h]	0.507	0.458	0.292	0.271
(Min-Max)	(0.333-1.50)	(0.167-1.50)	(0.167-0.50)	(0.167-0.333)
$AUC_{0-\infty}$ [ng·h/ml]	2335.14	1086.23	3912.90	1748.52
VK (%)	43.91	43.55	36.97	39.14

The values are mean values and coefficient of variation (VK) and/or minimum and maximum.

Plasma concentrations of the enantiomers following administration of one film-coated tablet of Thioctacid 600 HR in a Concentration-Time diagram:

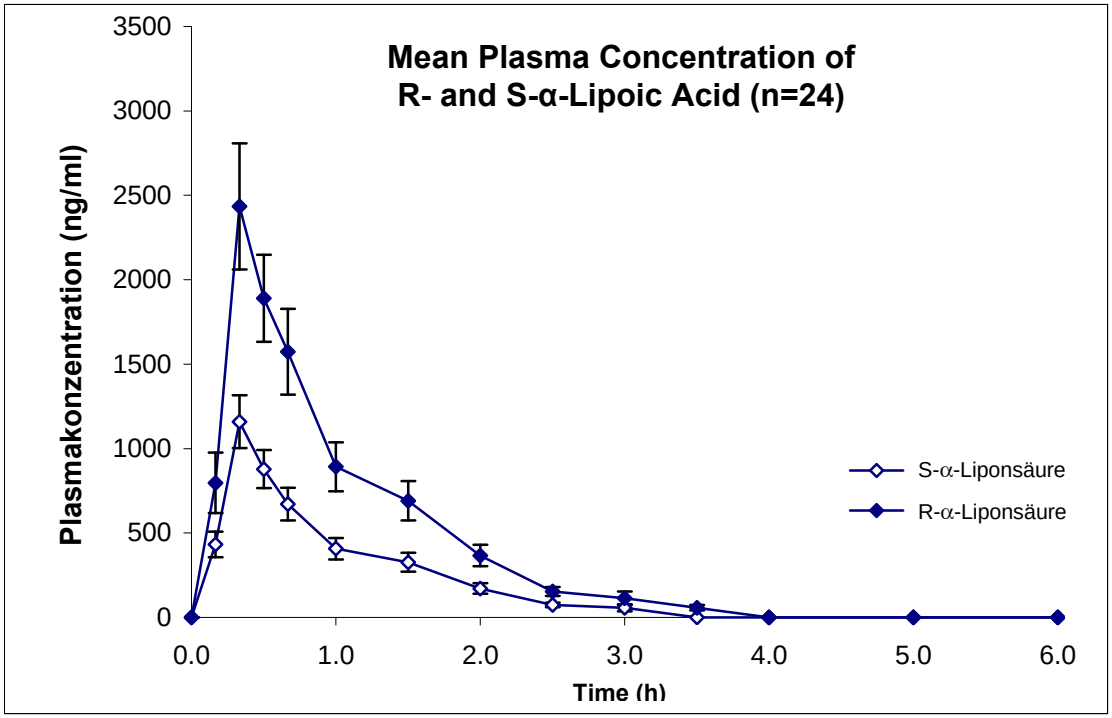
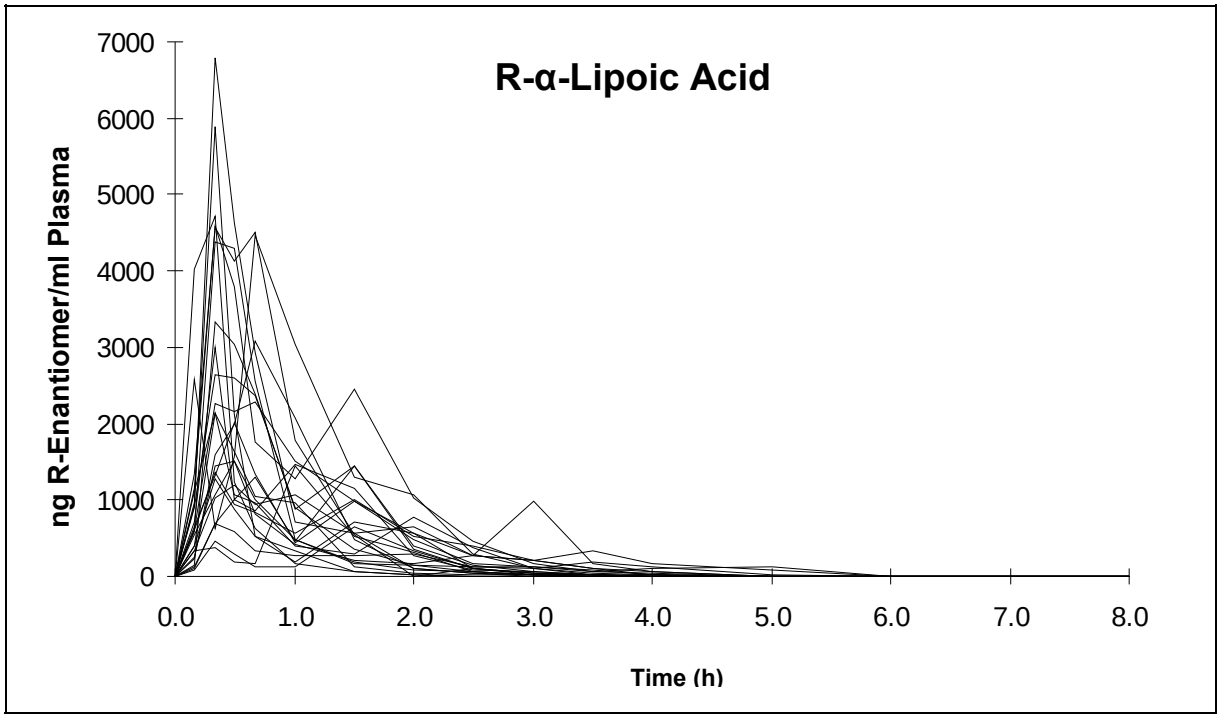


Figure 1: Mean plasma concentrations (arithmetic mean ± SEM) of R- and S-α-lipoic acid in 24 healthy subjects (12 male and 12 female) following oral single dose of 600 mg of racemic alpha-lipoic acid in form of one film-coated tablet of Thioctacid 600 HR.



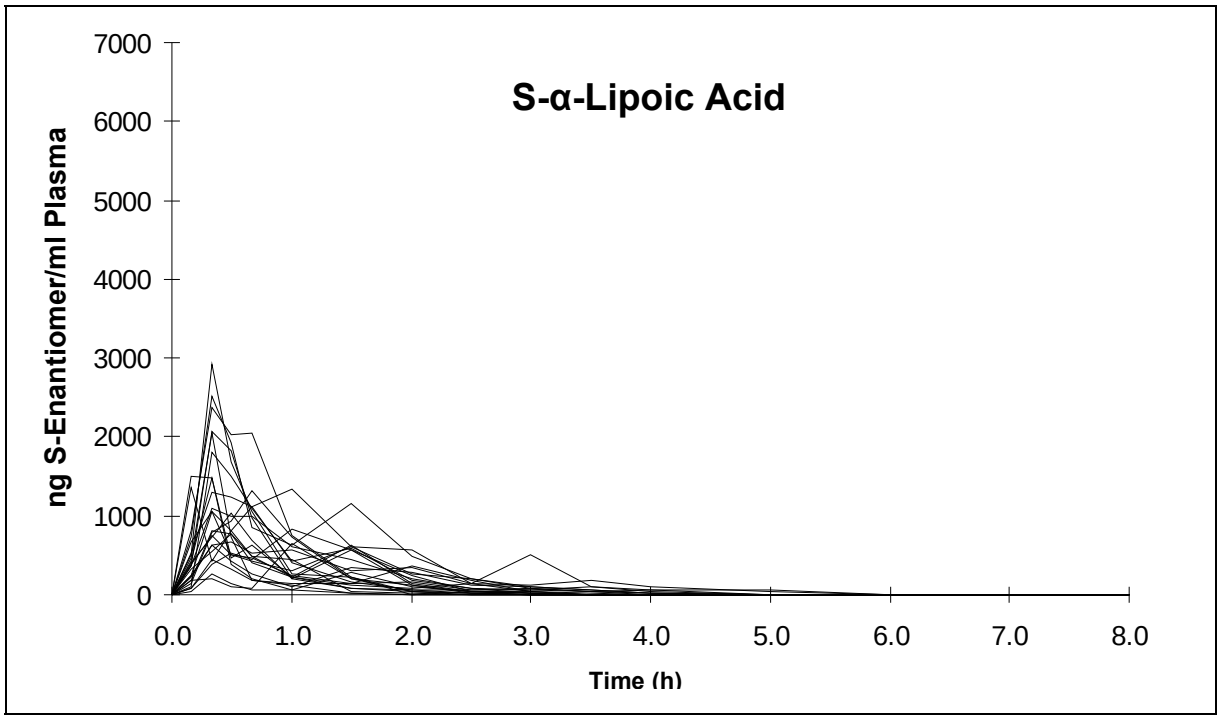


Figure 2: Plasma concentrations of 24 healthy subjects (12 male and 12 female) following oral single dose of 600 mg of racemic alpha-lipoic acid in form of one film-coated tablet of Thioctacid 600 HR.

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 alpha-lipoic acid from a carcinogenicity study. A study with regard to a tumour-promoting effect von alpha-lipoic acid in relation with the carcinogen N-Nitroso-dimethyl amine (NDEA) came to a negative result.

c) Reproductive toxicity

In the rat, alpha-lipoic 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

Poly(O-2-hydroxypropyl)cellulose (5.0-16.0 % hydroxypropoxy groups), Magnesium stearate, Hydroxypropyl cellulose, Hypromellose, Macrogol 6000, Talc, Titanium dioxide (E 171), Quinoline yellow, Aluminium salt (E 104), Indigo carmine, Aluminium salt (E 132).

6.2 Incompatibilities

In vitro, alpha-lipoic acid does react with metallic ion complexes (e. g. with Cisplatin). Alpha-lipoic acid enters into difficultly soluble complex combinations with sugar molecules (e.g. laevulose solution).

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Not all pack sizes may be marketed.

Container
Amber glass bottle, hydrolytic class III, with originality closure from polyethylene
Outer packaging
Folding box containing a package leaflet

Pack sizes
Original packs containing 30 (N1), 60 (N2) and 100 (N3) film-coated tablets
Hospital pack contains 400 (10x40) film-coated tablets
Samples not for sale

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Germany: 6372026.01.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/12/1999 – 26/10/2007

10. DATE OF REVISION OF THE TEXT

02/2010