Thioctic acid

Thiogamma® 600 oral

600 mg Film-Coated Tablet
Antioxidant

PRODUCT DESCRIPTION:
The developed product is an oblong film-coated tablet.

FORMULATION:
Each tablet contains:

Thioctic Acid (alpha-Lipoic Acid)……..	600 mg
Excipients (as follows)	
Hypromellose (Hydroxypropylmethyl-cellulose 5-6 mPa*s)…..……	25 mg
Silica, colloidal anhydrous……..……	25 mg
Cellulose, microcrystalline……	49 mg
Lactose monohydrate……	49 mg
Carmellose sodium (Carboxymethyl-cellulose sodium)……	6 mg
Talc……	26.364 mg
Simethicone Emulsion 30%……..……	3.636 mg
Magnesium stearate……	16 mg
Macrogol 6000……	0.6 mg
Hypromellose (Hydroxypropylmethyl-cellulose 6 mPa*s)…..……	2.8 mg
Talc…..……	2 mg
Sodium laurilsulfate…..……	0.025 mg

INDICATION:
For treatment of patients with peripheral diabetic polyneuropathy.

DOSAGE, METHOD AND LENGTH OF ADMINISTRATION
Individual and Daily Doses
In the case of sensory disturbances associated with diabetic polyneuropathy, the following daily dose is recommended for adults:
The daily dose is 1 Thiogamma 600 oral film-coated tablet (equivalent to 600 mg of alpha-Lipoic acid), which is taken approximately 30 minutes before the first meal.
In cases of severe sensory disturbances, infusion therapy with alpha-Lipoic acid can be carried out initially.
Elderly - no dose adjustment
Renal Impairment - dosage adjustment is necessary
Hepatic Impairment - limited experience. Therefore, use with caution.

Method and Length of Administration
Thiogamma 600 oral film-coated tablets should be taken whole and with plenty of water on an empty stomach. The tablets should not be chewed. The simultaneous consumption of food may hinder resorption. It is therefore particularly important in patients with a prolonged stomach emptying time that the tablets are taken half an hour before breakfast.
As diabetic polyneuropathy is a chronic disease, long-term therapy with Thiogamma® 600 oral may be required.
A fundamental requirement of diabetic polyneuropathy therapy is optimum adjustment of the diabetes.

CONTRAINDICATIONS
Thiogamma 600 oral is totally contraindicated in patients with known hypersensitivity to alpha-Lipoic acid or any of the other constituents of Thiogamma 600 oral.
Note: Children and adolescents (under 18 years old) should not be treated with Thiogamma 600 oral, as there is no clinical experience of this age group.

ADVERSE DRUG REACTIONS
In the assessment of side effects the following frequencies are used:

Very common	(>1/10)
Common	(>1/100 to <1/10)
Uncommon	(>1/1,000 to <1/100)
Rare	(>1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Nervous system disorders:
Very rare: Change in taste sensations

Gastrointestinal disorders
Very rare: Nausea, vomiting, gastrointestinal pain and diarrhoea.
Immune system disorders
Very rare: Allergic reactions (such as skin rash, hives (urticaria) and itching)
Not known: Insulin autoimmune syndrome (see section "WARNINGS AND PRECAUTIONS")
Metabolism and nutrition disorders
Very rare: Because of improved glucose utilization, a fall in blood sugar levels may occur. Symptoms similar to those of hypoglycaemia have been described such as vertigo, diaphoresis, headache and altered visual perception.

OVERDOSE AND TREATMENT
In cases of overdose patients may experience nausea, vomiting and headaches.

After the accidental or suicidal intake of oral doses of between 10 and 40 g of alpha-lipoic acid in conjunction with alcohol, severe intoxications - some of which had a lethal outcome - have been observed. The clinical toxicological profile may manifest itself initially in psychomotor restlessness or clouding of consciousness and is typically associated subsequently with generalised seizures and the formation of lactic acidosis. There have also been descriptions of hypoglycaemias, shock, rhabdomyolysis, haemolysis, disseminated intravascular coagulation (DIC), bone marrow depression and multi-organ failure as the intoxication consequences of high doses of alpha-Lipoic acid.

Therapeutic Measures in Cases of Intoxication:
Even if there is only a suspicion of substantial intoxication with alpha-Lipoic acid (e.g. > 10 tablets of 600 mg each in the case of adults and > 50 mg/kg of body weight in children) the patient should be admitted to a clinic immediately and general treatment measures for cases of poisoning initiated (e.g. induced vomiting, gastrolavage, active charcoal etc.). The treatment of generalised seizures, lactic acidosis and all other life-threatening consequences of intoxication must be carried out in line with the principles of modern intensive care and in accordance with the symptoms. The benefits of the use of haemodialysis, haemoperfusion or filtration techniques in the forced elimination of alpha-Lipoic acid have not been conclusively demonstrated.

WARNINGS AND PRECAUTIONS
Patients with the rare hereditary galactose intolerance, glucose-galactose malabsorption or Lapp lactase deficiency should not take Thiogamma 600 oral.
Cases of Insulin Autoimmune Syndrome (IAS) have been reported during treatment with alpha-lipoic 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 alpha-lipoic 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 "ADVERSE DRUG REACTIONS").

INTERACTIONS WITH OTHER MEDICATIONS AND OTHER FORMS OF INTERACTION
Loss of efficacy of cisplatin during simultaneous treatment with Thiogamma 600 oral.

Thioctic Acid (Alpha-Lipoic acid) is a metal chelator and for fundamental reasons should not therefore be administered at the same time as metal compounds (e.g. iron preparations, magnesium preparations, milk products due to the calcium content). If the entire daily dose of Thiogamma 600 oral is taken 30 minutes before breakfast, iron and magnesium preparations can be taken at lunchtime or in the evening.

The blood-sugar lowering effect of insulin and oral anti-diabetics may be reinforced. For this reason, close monitoring of blood sugar levels is indicated, particularly during the initial phase of alpha-Lipoic acid therapy. In order to avoid the symptoms of hypoglycaemia it may prove necessary in individual cases to reduce the insulin dose or the dose of the oral anti-diabetic.

Note: The regular consumption of alcohol represents a significant risk factor for the development and progression of neuropathic clinical pictures and may therefore prevent the success of treatment with Thiogamma 600 oral. Patients with diabetic polyneuropathy are therefore recommended as a matter of principle to avoid the consumption of alcohol as much as possible. This also applies to therapy-free periods.

PREGNANCY AND LACTATION
It is a general principle of pharmacotherapy that during pregnancy and the lactation period medicinal products should only be used after careful consideration of the risks and benefits.

Pregnant women and those who are breast-feeding should therefore only undergo treatment with alpha-Lipoic acid if the doctor determines that this is strictly indicated, even though reproduction toxicological studies have not shown any indications that fertility or early embryo development are affected and the medicinal product has not been found to have any embryotoxic properties.
It is not known whether alpha-Lipoic acid passes into the mother's milk.

PRECLINICAL SAFETY DATA
Toxicological Properties:
a) Acute and chronic toxicity The toxicity profile is characterised by symptoms which affect both the vegetative nervous system and the central nervous system. After repeated application the other target organs of toxic doses are mainly the liver and kidney.
b) Mutagenic and Tumour-Producing Potential: Investigations into mutagenic potential have not provided any indications of gene or chromosome mutations. A cancerogenicity study after the oral application of alpha-Lipoic acid to rats did not bring to light any indications of a tumour-producing potential. A study on a tumour-promoting effect of alpha-Lipoic acid in conjunction with the cancerogenic substance N-nitroso-dimethyl amine (NDEA) proved negative.
c) Reproduction Toxicity: Alpha-Lipoic acid does not have any effect on

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fertility or early embryo development in rats up to the maximum investigated oral dose of 68.1 mg/kg.
After intravenous injections to rabbits no deformation-producing properties are found up to the maternal-toxic dose range.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: neuropathy preparation
ATC Code: A16AX01
Mechanism of action
Alpha-Lipoic acid is a vitamin-like, but endogenously formed substance with a coenzyme function in the oxidative decarboxylation of alpha-keto acids and a powerful antioxidant. Both alpha-Lipoic acid and its reduced form dihydro-Lipoic acid (DHLA) are capable of scavenging a variety of reactive oxygen species. DHLA is cabable of directly regenerating ascorbic acid from dehydroascorbic acid and indirectly regenerating vitamin E.

Pharmacodynamic effects
As a result of the hyperglycaemia caused by diabetes mellitus there is an accumulation of the glucose on the matrix proteins of the blood vessels and the formation of so-called "advanced glycosylation end products". This process results in a reduction in endoneural blood flow and endoneural hypoxia/ischaemia, which is associated with the increased production of free oxygen radicals which damage the peripheral nerve. A depletion of antioxidants such as glutathione has also been found in the peripheral nerve.

In experiments performed on rats, alpha-lipoic acid interacted with these biochemical processes by reducing the formation of advanced glycosylation end products, improving endoneural blood flow, raising physiological antioxidant levels of glutathione and acting as an antioxidant for free oxygen radicals in the diabetic nerve.
These effects observed in the experimental situation indicate that the functionality of the peripheral nerves can be improved by alpha-lipoic acid. This applies to sensory disturbances in diabetic polyneuropathy, which may manifest themselves as dysaesthesias and paraesthesias, such as a sensation of burning, pain, numbness and pins and needles. Furthermore, patients who received ALA experienced significant improvement in insulin sensitivity.

Clinical efficacy and safety
ALA has been studied extensively for the treatment of diabetic polyneuropathy (DN). Eleven, prospective, randomized, double-blind, placebo-controlled trials with more than 1500 patients have been conducted on the effect of ALA for DN. The studies were performed with both oral and intravenous administration of ALA. In four studies, the effectiveness was investigated when administered orally, in four studies after intravenous administration and in three trials, ALA was applicated initial intravenously and then orally. Alpha-Lipoic acid was found to have favourable effects on the investigated symptoms of burning, paraesthesia, numbness and pain. Moreover, the results from 14 uncontrolled studies with ALA in patients with DN are available.
ALA appears to be safe in dosages generally prescribed clinically. The adverse reaction profile is comparable to placebo, except of the high doses (1200 mg), and does not show certain, undesirable effects, which might restrict its use in certain patients. To date, ALA in doses up to 600 mg daily has been well tolerated. Minor side effects include skin reactions and gastrointestinal effects, such as nausea and vomiting, and allergic reactions. However, these effects have only been observed in a small percentage of subjects. At start of the therapy, a temporary worsening of neuropathy may occur.

Pharmacokinetic Properties
Absorption
Alpha-lipoic acid is rapidly and almost completely absorbed from the gastrointestinal tract in humans. Following oral administration approximately 87% of a dose of ALA is absorbed. The bioavailability is about 20-30% that of an intravenous dose. Peak serum ALA concentration of 4.44±3.65 Hg/ml occur within 0.31 ± 0.1 hours following oral administrationof a single 600 mg dose. Food intake significantly reduced the bioavailability of ALA. Dose proportionality for both enantiomers of ALA was demonstrate after p.o doses of 50-600 mg.

Distribution
ALA is well distributed in tissue. Studies with 14C-labeled lipoate in rat, administered either i.p. or oral, the highest concentrations are found in the urine, as respiratory 14CO2, and in the tissues, of which highest concentrations were detected in the liver, muscle, intestine and nerves.

Biotransformation
ALA was shown to be metabolized largely through ß-oxidation of the valeric acid side chain. Major metabolites identified were bisnorlipoic acid, tetranorlipoic acid, and ß-hydroxy-bisnorlipoic acid. Reduction of exogenous lipoic acid to dihydrolipoate occur in several mammalian cells and tissues. The serum elimination half-life after oral administration of 600 mg is rapid with a value of 34.79 ± 8.74 min on day one and 31.90 ± 7.47 min on day 4.

Excretion
ALA is excreted mainly in the urine within 24 hours of a single oral or parenteral dose. But the kinetic results revealed that urinary excretion of ALA and five of its main metabolites does not play a significant role in the elimination of ALA. Therefore, biliary excretion, further electrochemically inactive degradation products, and complete utilization of ALA as a primary substrate in the endogenous metabolism should be considered.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
For suspected adverse drug reaction, please report to the FDA: www.fda.gov.ph

STORAGE:
Store at a temperatures not exceeding 30°C, in a dry place. Protect from sunlight and moisture.
Keep out of reach of children.

AVAILABILITY:
Thiogamma 600 Oral 600 mg is available in Alu-PVC blister pack of 10 tablets;
Box of 30's, 60's and 100's.

Manufactured by:
Dragenopharm Apotheker Püschl GmbH
Göllstr. 1, 84529 Tittmoning, Germany

For:
Wörwag Pharma GmbH & Co. KG
Flugfeld-Allee 24, 71034 Böblingen, Germany

Imported & Distributed by:
Metro Drug, Inc.
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa City, Laguna, Philippines

Reg. no.: DR-XY46038

Date of First Authorization: 25 Sep 2017

Date of Revision of Package Insert: 27 Jul 2023

Wörwag Pharma GmbH & Co. KG,
Flugfeld-Allee 24, 71034 Böblingen

VNr. 04-0923-00 / 601906 / PH

148 x 420 mm / 8 pt / PC 23409
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customer:	Wörwag Pharma GmbH & Co. KG
product:	**Thiogamma 600 oral**
	Gebrauchsinformation / Leaflet
country:	Philippines **(PH)**
dimensions:	148 x 420 mm – **Dragenopharm**
font:	Marselis Pro / DIN Next CYR (Min. size 8pt.)
colors:	■ black
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date:	02.05.2017 / 08.05.2017 / 19.05.2017 / 24.05.2017 / 19.06.2017 / 26.07.2018 / 17.09.2018 / 12.11.2018 / 18.11.2019 / 26.11.2019 / 04.02.2021 / 10.02.2021 /		
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31.08.2023	7	04-0923-00	CMa (new design)
06.09.2023	1	04-0923-00	CMa
07.09.2023	1	04-0923-00	CMa
19.09.2023	1	04-0923-00	JuS