RISK PROFILE

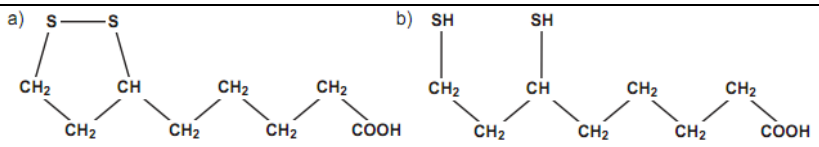
Alpha lipoic acid (ALA)

CAS No.1077-28-7

Date of reporting 13.02.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	Alpha lipoic acid [1,2-Dithiolane-3-pentanoic acid, (+/-)-]
INCI	DL-thiotic acid
Synonyms	Thiotic Acid or Thioctic Acid
CAS No.	1077-28-7 / DL-alpha lipoic acid 62-46-4
EINECS No.	214-071-2
Molecular formula	$C_8H_{14}O_2S_2$
Chemical structure	 **Fig. 1.** Lipoic acid (**a**) and its reduced form – dihydrolipoic acid (**b**) The carbon atom at C6 is chiral and the molecule exists as two enantiomers R-(+)-lipoic acid (RLA) and S-(-)-lipoic acid (SLA) and as a racemic mixture R/S-lipoic acid (R/S-LA). Only the R-(+)-enantiomer exists in nature and is an essential cofactor of four mitochondrial enzyme complexes (Singh & Jialai, 2008). The R-isomer [CAS No. 1200-22-2] is the natural co-factor of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in mitochondria (Hermann et al., 1996), whereas R/S-α-lipoic acid [CAS No. 1077-28-7] is available as a reagent from SigmaAldrich at 99% purity (Drugs [online]).
Molecular weight	206.3 g/mol
Contents (if relevant)	

Physiochemical properties	Appearance: light yellow to yellow powder Solubility water: DL-form of ALA sparingly soluble Solubility: 50 g/l at 20 °C Ethanol Melting point: 60 – 62 ^{o}C Boiling point: 160 - 165 ^{o}C Vapor pressure: 3E-6 (25 C) Density: 1.343 g/cm^{3} Partition coefficient P_{ow}: 2.16

2. Uses and origin

Uses	➢ **Cosmetic products:** ***Functions according to*** o *CosIng database*: "Antioxidant" – "Inhibits reactions promoted by oxygen, thus avoiding oxidation and rancidity" o *Other:* Anti-wrinkle facial skin care[1] ***Concentrations being applied*** Anti-wrinkle cream typically contains 5% ALA (Beitner, 2003) ***Frequency of use*** *(ref: EWG)* o facial moisturizer/ treatment (55 products) o anti-aging (54 products) o around-eye cream (14 products) o sunscreen: moisturizer (12 products) o moisturizer (10 products) The German database CodeCheck[2] embraces 30 cosmetic products containing ALA. Except for a shampoo and a hair coloring product those mentioned are in the category anti-aging products. ➢ **Food** ALA is typically present in red meat, kidney, heart, and liver, and to a lesser extent in vegetables (e.g. potatoes, carrots, broccoli and kohlrabi). Good sources are yeast and liver. The amounts occurring naturally in foodstuffs are, however, at a suppressed level of not more than around 3 ppm in the richest sources (EFSA 2010). Hence, appreciable amounts of ALA are not consumed in usual Western diet. Thus, the *primary* source of ALA is from *dietary supplements* intake amounts being in the range 50 – 600 mg per day. (Shay et al., 2009).

[1] This is according to an application to the Norwegian medicinal products agency dated 7 June 2004 (Ref no of agency: 04/6854). The company in question asked for allowance to use this substance up till 5 %.
[2] http://www.codecheck.info

	Because ALA either from dietary sources or as a nutritional supplement is readily absorbed, metabolized and excreted, negligible free ALA is retained in tissues in the post-fed state. Thus, the direct sustained *in vivo* effect of ALA has been questioned. According to a survey of 685 herbalists, ALA was one of the 10 most frequently recommended dietary supplements due to its efficacy in reducing high blood sugar levels, but a cause and effect relationship has not been established between the usage of ALA and increase in insulin sensitivity (EFSA opinion, 2011). ➢ **Medicinal products** Intravenous and oral ALA is approved for therapy of diabetic neuropathy and retinopathy in Germany and has been used for over 50 years (Shay et al., 2009; Bilska & Włodek, 2005; Singh & Jialal, *2009).* Neuropathy is a painful condition where the myelin sheaths of nerve endings are damaged or disintegrated. Topical and oral administration of ALA may help treat inflammatory skin conditions such as atopic and contact dermatitis as well as psoriasis (Venkatraman et al., 2004). See Annex 1 for doses of ALA reported in clinical trials. Various other unproved uses to alleviate various medical conditions are listed in Annex 2 (see also UpToDate [online]). ➢ **Other products** ALA has been researched for its effect on insulin sensitivity, glucose metabolism, and diabetic neuropathy (NIH [online]. A potential therapeutic role for ALA in dementia has been postulated, but according to a Cochrane report its use in the treatment of dementia is currently not recommended (Klugman et al., 2004). A protective role for ALA from the damaging effects of radiation has been suggested (Geronova Research [online]).
Origin Natural (exo /endo) Synthetic	Discovered in 1951, ALA is well known as an essential sulfur-containing cofactor for enzyme complexes involved in mitochondrial ATP production. ALA is synthesized in the human body and therefore not classified as an essential nutrient. ALA is a cyclic disulfide antioxidant that interconverts with its reduced dithiol form, DHLA. The oxidized ALA and its reduced form DHLA has a standard reduction potential of -0.32 V, making DHLA one of the most potent naturally occurring antioxidants (Shay et al., 2009). One of its most important characteristics is that it is both fat-soluble and water-soluble. This enables it to provide antioxidant protection in a much wider range of physiological environments throughout the body (Moini et al., 2002). Additional information on ALA functions is given in Annex 2b. Because ALA only transiently accumulates *in vivo* and is rapidly catabolized, questions have been raised whether ALA could augment endogenous antioxidant capacity on sustained basis.

3. Regulation

Norway	Alowed at a concentration of 5 % in anti-aging products, but in no other cosmetics products. This regulation will be lifted 11 July 2013
EU	No regulation
Rest of the world	***Japan*** Maximum allowed concentration in leave- on and rinse-off cosmetics: 0,01 % Products meant to be used on mucosa: forbidden –reference: Japanese Standards for Cosmetics [online]. ALA is approved for use in food in Japan from 2005.

4. Relevant toxicity studies

Absorption Skin	A selenotrisulfide derivative of lipoic acid was found to be efficiently absorbed topically into pig skin (Alonis et al., 2006). The skin penetration was attributed to lipoic acid, since the selenium component was poorly absorbed in skin *per se*. Podda et al. (1996) reported that topically applied ALA readily penetrated murine skin, and was reduced to DHLA, potentiating the antioxidant protection of skin. Freisleben et al. (1994) provided indirect evidence for skin penetration of dihydrolipoate (i.e. the reduced form of ALA). Available data do not permit estimation of skin penetration rates applicable to systemic exposure calculations.
GI tractus	GI: Rapid gastrointestinal uptake followed by equally rapid clearance (Shay et al., 2009, and references therein).
Distribution	Transient accumulation in the liver, heart and skeletal muscle, but also other tissues (e.g. brain) (Shay *et al*., 2009). Free ALA is not normally detected in plasma (Hermann et al., 1996) or in skin (Podda *et al*., 1994). Following oral or parenteral infusion, it remains in plasma about 30 minutes and is cleared by liver during first pass (Hermann *et al*., 1996). Similar rapid clearance may also occur after percutaneous absorption. ALA exhibits dose proportionality between 50 and 600 mg (Breithaupt-Grøgler *et al*., 1999). Bioavailability is approximately 29% after ingestion of 200 mg ALA (Teichert *et al*., 1998).
Metabolism	ALA is synthesized de novo from an 8-carbon fatty acid (octanoic acid) and cysteine (as a sulfur source) in the liver. Its catabolism also takes place in the liver. β-oxidation is the major route by which ALA is metabolized *in vivo* (Shay et al., 2009

Excretion	ALA and its metabolites are readily excreted, primarily in the urine (Shay et al., 2009); 98% of radiolabeled ALA is excreted in urine within 24 hours (Schupke *et al*., 2001, cited in Shay *et al*., 2009). Rapid clearance ($T_{1/2}$ ~ 30 min) and metabolic transformation of oral ALA by hepatocytes seems to be integral to the mechanisms of action and to prevent tolerability and safety risks of ALA, especially during long term therapy (Carlson *et al*., 2008). Following oral or parenteral infusion, ALA remains in plasma about 30 minutes and is cleared by liver during first pass (Hermann *et al*., 1996). Experimental or clinical evidence is lacking as concerns clearance after percutaneous absorption.
Local toxic effects Irritation Sensitivity	Dermatologic reactions (rashes) have been reported with ALA (UpToDate [online]). Allergic contact dermatitis has occurred after an ALA anti-wrinkle cream was used, as described in three case-reports. Further testing in two of three reported cases gave a strongly positive reaction to 5% ALA /lower level 0.025% (two cases) and 0.5% (one case), respectively. 10 healthy middle-aged females tested without any allergic or irritant reactions to ALA at doses of 5%, 2.5% and 0.5% (Bergqvist-Karlsson *et al.,* 2006). 15 other reports on suspected adverse skin reactions to ALA (5%) were submitted to the adverse reaction reporting system of the Department of Cosmetics Section of the Swedish Medical Products Agency (cited in Bergqvist-Karlsson *et al.,* 2006). As concerns one 5% product placed on the market in Sweden the Swedish Medical Products Agency received all in all 25 reports over a period of 7 years from 2002 till 2009. After the company in question lowered the concentration from 5 to 3 % in 2010 no further reports have been received (Medica Nord 2012). Beitner (2003) reporting about a Swedish clinical efficacy test involving a 5 % ALA containing cream and 32 female volunteers, states as follows as concerns side effects observed. *"In this study we have noticed that local irritation on application of 5% ALA is common during the first weeks of treatment"*. Seemingly, irritation occurred transiently in 85 % of the participants. The author compares these side effects to those commonly seen in connection with topical medicinal usage of retinoic acid[3], judging them to be milder in that scaly erythema combined with swelling of the skin did occur only rarely. Rash and desquamation occurred in 10% of the participants. Beitner choose to use 5 % ALA because this concentration level appeared optimal treating photo-aged skin. The 25 cases having been reported to the Swedish cosmetovigliance system relates to in-market use of the product tested by Beitner and that was launched onto the Scandinavia market in 2002. These 25 cases were reported voluntarily by Swedish dermatologs and so should not be confused with the side effects observed by Beitner in his study. Cosmetovigilance systems run by governmental agencies are characterized by severe underreporting[4]. Hence, it is beyond discussion that the cases reported most probably represents only a minute fraction

[3]The use of retinoic acid is prohibited in cosmetics products mainly because of the irritation effect (SCC).

[4] This concerns all the three established European cosmetovigilance systems; in France, Sweden and Norway

	of all the cases actually occurring in consumers that made use of the named product – or similar products involving a high ALA concentration. Apparently, in the public domain there is a void as concerns data on sensitization potency – this being data obtainable by the usual tests in this connection; LLNA (EC B.42, OECD Guideline 429); GPMT) (EC B.6, OECD 406) or the Buehler test [EC B.6, OECD 406].
Systemic toxic effects Acute	There is marked differences among species regarding safety levels for acute oral ALA intake; dogs: LD_{50} of 400 – 500 mg/ kg bw (Packer et al., 1995; cited in Shay et al., 2009); mice: LD_{50} of 500 mg /kg; rats: LD_{50} >2000 mg /kg bw. Lower dosages (20 mg/kg) given intraperitoneally to severely thiamine-deficient rats proved fatal. The lethal effect was prevented when thiamine was administered with LA (Gal, 1965). ALA was found to be 10 times more acutely toxic to cats than in humans, dogs, or rats, with a maximum tolerated dose <30 mg/kg with regard to hepatocellular toxicity (Hill et al., 2004). The difference in toxicities between the two species is thought to be because ALA is sustained for significantly longer periods of time in the plasma of cats. This is presumably due to lower rates of hepatic metabolism and excretion. The most frequently reported side effects to oral ALA supplementation are allergic reactions affecting the skin, including rashes, hives and itching (Packer et al., 1995). A NOAEL of 61.9 mg ALA/kg bw /day was calculated following chronic administration of ALA to male and female rats for four weeks by gavage, based on slight alterations in liver enzymes as well as histopathological effects on the liver and mammary gland (Cremer et al., 2006a).
Repeated dose	A two-year toxicity study with oral supplementation of ALA in male and female Sprague-Dawley rats did not show any adverse effects with regard to weight, histopathology and blood chemistry up to 60 mg ALA/ kg bw /day (Cremer et al., 2006b). In treatment groups, mortality was slightly lower than in the control group. At higher chronic doses of ALA (180 mg /kg), the only notable findings were that body weight gain and food consumption were decreased, but no gross pathology was evident. *Thus, a NOAEL of 60 mg /kg bw /day ALA has been established for long-term ALA supplementation in rats* *Applying a bio-availability of 30 % a systemic NOAEL via oral administration of 18 mg/kg bw/day is estimated.*
Mutagenicity /genotoxicity	- ALA was not mutagenic in the Ames assay (NIEHS, 2004). - ALA was negative in Salmonella typhimurium TA97, TA98, TA100, and TA1535 with and without rat and hamster liver S-9 (NTP, 2004). - ALA was negative in Salmonella (A06994) test (NTP, 2004).
Carcinogenicity	The study by Cremer et al (2006b) further demonstrated that ALA had no carcinogenic potential in rats at doses up to 180 mg/kg/day. ALA did not significantly change tumour frequencies, induction times, or histology of liver and oesophageal tumours in rats (Habs et al., 1989, cited in NIEHS, 2004). Moreover, ALA had no effect on tumour growth in NMRI mice implanted with Ehrlich ascites carcinoma (NIEHS, 2004). A decrease in survival time was believed to be due to high dose of ALA administered.

Reproduction toxicity / teratogenicity Other effects	There is no published evidence for reproduction toxicity caused by ALA: on the contrary, ALA administered i.p. to pregnant diabetic rats reduced the number of malformations and fetal loss when compared to the offspring of untreated diabetic rats. ALA also protected against growth reduction of diabetic embryos (Wiznitzer et al., 1996, cited in NIEHS, 2004). ***Drug Interactions*** A total of 40 drugs (135 brand and generic names) are known to interact with ALA. These interactions are classified as 'minor' drug interactions. It is recommended not to take ALA with any of the following medications without medical guidance (Drugs [online]). - levothyroxine (Synthroid) and other thyroid medications; - insulin or diabetes medications such as metformin (Glucophage), glyburide (DiaBeta, Glynase), and others. See also Annex 3

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	18 mg /kg bw /day (Systemic via oral administration / animal data)
Exposure cosmetic products	SED: usage level of ALA at 5 % (illustrative purposes) : Face cream: (24.14 mg/kg bw/day * 0.05) = 1.2 mg/ kg bw /day Hand cream: (32.70 mg/kg bw/day * 0.05) = 1.6 mg /kg bw /day Body cream: (123.20 mg/kg bw/day * 0.05) = 6.2 mg /kg bw /day (cf. default values in SCCS Notes of Guidance, Table 3, 7th revision, SCCS//1416/11).
Margin of Safety (MoS)	MoS (NOAEL/SED): MoS (Face cream): 18 /1.2 = 15.0 MoS (hand cream): 18 /1.6 = 11.3 MoS (body cream): 18 /6.2 = 2.9

6. Other sources of exposure than cosmetic products

Food stuffs	The primary source of ALA is dietary supplements, ranging from 50 – 600 mg/day (Shay et al., 2009). Oral ALA is reported to be well tolerated in doses up to 600 mg/day (UpToDate [online]). Applying a default value of 60 Kg bw and taking into account a bio-availability of 30 % these daily oral doses corresponds to SED values via supplements amounting to. 0,25 – 3 mg/kg bw /day - normal usage pattern At intakes exceeding ((1200/60) x 0,3 =) 6 mg/kg/day different acute adverse effects have been observed; nausea, vomiting, dizziness, headache, skin rash, muscle cramps and the sensation called pins and needles (cf. "Physicians Desk Reference) Presumably, the systemic NOAEL in man *via* oral intake is much

	lower than 6 mg/kg/day (3 mg/kg/day?).
Pharmaceuticals	In select clinical trials, e.g. ALADIN (I, II and III), SYDNEY (I and II), and ORPIL, ALA have been used up to 2400 mg /day with no adverse effects vs. placebo (see Annex 1 and "Adverse side effects" below).
Other sources	
Adverse side effects - from uses other than cosmetics	Unless otherwise cited, this information is from 'Medical Content' created by 'Natural Standard' - based on a systematic review of scientific literature edited and peer-reviewed by contributors to the Natural Standard Research Collaboration and 'Faculty of the Harvard Medical School' (NationalStandard [[online]). Few side effects of ALA have been reported. Allergic skin conditions are among the reported adverse reactions of oral LA administration in humans. The most common complaints as mentioned above generally occurred in studies at doses of 1200 - 1800 mg (normal supplement doses are between 50 and 500 mg per day). Select clinical trials using ALA up to 2400 mg /day with *no adverse effects vs. placebo* are listed in Annex 1, e.g. ALADIN (I, II and III), SYDNEY (I and II), and ORPIL. Doses of 600 mg/day administered intravenously for three weeks did not show evidence of serious adverse effects. Oral doses of 1800 mg ALA for 6 months did not elicit significant adverse effects compared to placebo. ALA has been used in Germany for over 50 years as a therapy for diabetic neuropathy and retinopathy (Ziegler et al., 1995; 1999; Ziegler 2004). Some natural medicine experts discourage the use of ALA in people with underactive thyroids (hypothyroidism). Based on deaths seen in animal research, ALA should be avoided in patients with thiamine deficiency, a condition commonly linked to alcoholism. However, there are no specific studies in humans, so the risks of ALA use in people with these conditions are not clear (Juvenon [online]). It is recommended to use ALA cautiously among patients with type 2 diabetes, due to the possibility of changes in insulin sensitivity (UpToDate [online]). A case report of insulin autoimmune syndrome was reported in a woman who regularly took ALA 200 mg/day. After discontinuing ALA, hypoglycemia disappeared and the titer of anti-insulin antibodies was markedly decreased (Ishida et al., 2007). (About Alpha Lipoic Acid [online]). Although abundant evidence exists for the safety of ALA in moderate doses, ALA may mediate oxidative insult at higher doses or when administered intraperitoneally. E.g. intraperitoneal administration of a high chronic dose of 100 mg /kg bw /day ALA for 2 weeks in aged rats (~equivalent to 5 - 10 g/ day in humans), resulted in increased plasma lipid hydrogen peroxide levels and oxidative protein damage. LA-mediated protein damage was noted in rat heart and brain, whereas lipid peroxide levels were beneficially decreased in both organs (Cakatay & Kayali, 2005; Shay et al., 2009). <u>Interactions</u>: Medical supervision is needed if ALA is taken with medications for lowering blood sugar, e.g. metmorfin (Glucophage), glipizide (Glucotrol), and glyburide (DiaBeta), as there may be harmful interactions.

7. Assessment

ALA is popular in health store products both for internal use (e.g. dietary supplements) and in cosmetics. For example, 106 cosmetic products were registered in EWG cosmetic database (Sept 2011), including anti-ageing and anti-wrinkle creams. In a popular product line a formulation of 5% ALA is used in combination with Coenzyme Q10 and acetylcarnitine (QAL-100), and is marketed as an anti-wrinkle cream (Bergqvist-Karlsson et al., 2002; Beitner et al., 2003).

General toxicity
In human skin, there is evidence for efficient transdermal uptake of ALA, but more precise data on local metabolism and systemic bioavailability are lacking. Oral ALA is subject to rapid clearance as it remains in plasma only about 30 minutes and is cleared by liver during first pass (Hermann et al., 1996). It is still not known whether the route of ALA administration (dermal vs. oral) might be of importance for putative adverse effects (differences in clearance by liver during first pass).

A 2 year oral long-term safety study of ALA estimated a systemic NOAEL value of 18 mg/kg bw /day in rats, with no gross or histopathological changes although some liver and mammary gland changes occurred (Cremer et al., 2006). ALA generally seems to have few serious systemic side effects when used in recommended *systemic* doses of up till no more than 3 mg/kg bw/day (NIEHS, 2004; Shay et al., 2009).

Cosmetics
The clinical efficacy of a cream containing 5% ALA demonstrates a positive effect related to photoageing of facial skin (Beitner, 2003). However, it is recommended that people with allergies or hypersensitivities to ALA should avoid its use; e.g. allergic skin reactions (aka. contact dermatitis) have occurred after an ALA anti-wrinkle cream was used. Comparatively many skin reactions have been reported to the Swedish cosmetoviglance system this indicating ALA is a potent sensitizer – although quantitative data on that is so far missing. Apparently use of products containing 3 % ALA causes substantially less problems with skin reactions.

Applying the above mentioned premises – including the worst case assumption of a 100 % skin penetration rate - the contribution of ALA to systemic levels is roughly of about the same magnitude from oral intake. SEDs for facial cream, hand cream and body cream of 1.2, 1.6 and 6.2 mg /kg bw /day can be compared to 0,25 – 3 mg/kg /day for food supplements. The systemic NOAEL in humans may possibly be around 3 mg/kg bw/day. People enjoying each day both ALA-supplements and ALA cosmetics may risk being exposed to a total amount of ALA exceeding the NOAEL.

Applying the systemic NOAEL derived from animal (rat) experimentation of 18 mg/Kg bw/day MoS values estimated solely on the basis of the exposure for cosmetics amounts to 3 – 15. We are of the opinion that in order for ALA to be safely used in cosmetic products the MoS must be above 100. Hence, as is presently the situation in the marketplace, by and large, (5 % in the mentioned product types) the current usage of ALA in cosmetic is far from safe. We are then solely looking at the cosmetics as a source for exposure for ALA – which is not true for numerous consumers in the single market. There are also the popular ALA- food supplements to take into account. Doing that the risk situation seems even worse. In that connection we observe that the Japanese authorities have set the upper allowed concentration for ALA in leave- on and rinse-off cosmetics to no more than 0,01 % - and have forbidden it in mouth care products all together.

Medicinal products
The therapeutic use of ALA is not approved by regulatory agencies in US and generally not in Europe, with the exception of Germany, where clinical testing with oral ALA extends back to 1955 and ALA has been used for approx. 50 years as therapy for diabetic neuropathy and retinopathy.

Food supplements
The most frequently reported side effects to *oral* LA supplementation are allergic reactions affecting the skin, including rashes, hives and itching. Gastrointestinal symptoms, including abdominal pain, nausea, vomiting and diarrhea have also been reported. Malodorous urine has also been noted by people taking 1200 mg/day of LA orally (Yadav et al., 2005).

ALA has not been shown to have benefits when used as a nutritional supplement in healthy people (EFSA 2010, 2011). Since the 1990s, ALA has been used as a dietary supplement (typically at doses in the range of 100 – 200 mg/day), particularly because of its glucose lowering effects.
It should be avoided in pregnant or breast-feeding women, in people with thiamine deficiencies, and in children.

8. Conclusion

The current risk situation for the use of ALA in cosmetics is unsatisfactory. Usage of ALA at concentration not exceeding the below mentioned concentrations complies with the requirement that the MoS must be above 100 in order for these three different usages to be safe. We then base the risk evaluation on the NOAEL derived from animal experimentation, the observed oral bio-availability of 30 % and the default value of 100 % skin penetration (since no data exist).

- Face cream: 0.75 %
- Hand cream: 0.55 %
- Body cream: 0.15 %

- All other products: 0 %

At these much lower concentrations than are applied today in the marketplace, we would assume that problems with allergic skin dermatitis are avoided.

The different products should be labeled with following warning texts:

Not to be used on children
Not to be used during pregnancy or when breast-feeding
Not to be used suffering from type 2 diabetes

9. References

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10. Annexes

Annex 1: Clinical trials using ALA

Table 3

Select clinical trials using lipoic acid (LA).

Clinical Trial	Ref.	LA Dose administered to human subjects	Subjects receiving LA	Parameters measured†
Diabetes: ALADIN	[37]	100, 600, or 1200 mg, intravenous for 3 weeks	328	Neuropathic symptoms, HPAL, NDS
Diabetes: ALADIN II	[38]	a) 600 mg, intravenous, for 5 days + 600 mg, orally for 2 years b) 1200 mg, intravenous for 5 days + 1200 mg, orally for 2 years	a) 27 b) 18	NDS, electrophysiological attributes of the sural and tibial nerves
Diabetes: ALADIN III	[39]	a) 600 mg, intravenous, for 3 weeks + 1800 mg (600 mg *t.i.d.*) for 6 months b) 600 mg, intravenous, for 3 weeks + placebo for 6 months	a) 165 b) 173	TSS, NIS
Diabetes	[40]	a) 600 mg, oral, for 4 weeks b) 1200 mg (600 mg *b.i.d.*), orally for 4 weeks c) 1800 mg (600 mg *t.i.d.*), orally for 4 weeks	a) 19 b) 18 c) 18	Insulin-stimulated glucose disposal
Diabetes: ORPIL	[41]	1800 mg (600 mg *t.i.d.*), orally for 3 weeks	12	TSS, HPAL, NDS
Diabetes: SYDNEY	[42]	600 mg, intravenous, 5 days a week for 14 treatments	60	NCS, TSS, NIS, quantitative sensation test, autonomic test
Diabetes: SYDNEY II	[43]	a) 600 mg, orally for 5 weeks b) 1200 mg, orally for 5 weeks c) 1800 mg, orally for 5 weeks	a) 45 b) 47 c) 46	TSS, NCS, NIS
Diabetes: DEKAN	[44]	800 mg (200 mg *q.i.d.*), orally for 4 months	39	Cardiac autonomic nerve function
Diabetes	[45]	600 mg/day, orally for 3 months	33	Plasma lipid hydroperoxides, alpha-tocopherol, cholesterol
Multiple Sclerosis	[46]	a) 1200 mg *q.d.* b) 1200 mg (600 mg *b.i.d.*) c) 2400 mg (1200 mg *b.i.d.*)	a) 9 b) 7 b) 7	Serum LA, Matrix Metalloproteinase-9, and Intercellular Adhesion Molecule-1
Metabolic Syndrome: ISLAND	[47]	300 mg, orally for 4 weeks	15	Endothelial function and proinflammatory markers

†HPAL = Hamburg Pain Adjective List, NDS = Neuropathy Disability Score, NIS = Neuropathy Impairment Score, NSC = Neuropathic Symptoms and Change Score, TSS = Total Symptom Score

Intravenous administration of racemic LA at doses of 600 mg/day for 3 weeks and oral racemic LA at doses as high as 1800 mg/day for 6 months (Ziegler et al., 2004) and 1200 mg/day for 2 years (Ziegler et al., 1999) have been reported. For clinical trials, see Annex 1.

Annex 2: unproven effects of ALA associated with other uses

Unproven Uses

ALA has been suggested for many other uses, based on tradition or on scientific theories. However, these uses have not been thoroughly studied in humans, and there is limited scientific evidence about safety or effectiveness. Some of these suggested uses are for conditions that are potentially very serious and even life-threatening. You should consult a health care professional before taking ALA for any unproven use.

Aging (memory enhancement) Alzheimer's disease Amanita poisoning Antioxidant Atherosclerosis (clogged arteries) Atopic dermatitis Bile flow Bone loss Cancer Cerebrovascular disease Chemotherapy side effects Cognitive impairment Constipation Contact dermatitis Degenerative brain disorders Depression Diminished appetite (in cancer patients) Down syndrome Endothelial dysfunction Hearing damage (from certain drugs) Heart muscle injury (adriamycin-induced) Hepatitis C High blood pressure High cholesterol HIV Immune system stimulant Inflammation	Inflammatory vascular diseases Lead poisoning Liver disease (biliary cirrhosis) Mercury poisoning Metabolic disorders Metabolic syndrome Mitochondrial myopathies Mountain sickness Multiple sclerosis Muscular dystrophy (facioscapulohumeral dystrophy) Mushroom poisoning Nerve problems (from kidney disease) Neural tube defects Neurodegenerative diseases Nutritional supplement Obesity Pain after surgery Parkinson's disease Problems with blood sugar metabolism Psoriasis Retinal leukostasis Retinal ischemia/reperfusion Retinopathy Sepsis (prevention and treatment) Sickle cell anemia Smell disorders Stomach irritation Toxic kidney damage (oxaliplatin-induced) Vascular dementia Wilson's disease (a hereditary disorder)

http://www.intelihealth.com/IH/ihtIH/WSIHW000/8513/31402/347004.html?ddmtContent

Annex 2 b: Some ALA functions

Some of the functions of ALA are listed below:

-/ enantiomer form of ALA (see "Origin" in this section) is an essential cofactor for enzyme complexes involved in mitochondrial ATP production, notably pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase in the energy-producing Krebs cycle. http://bit.ly/nk8dS7

- Both ALA and DHLA are capable of reactive oxygen species scavenging. Neither species are active against hydrogen peroxide.

- ALA / DHLA appears to regenerate other endogenous antioxidants (e.g. vitamins C and E) (Packer, L et al., Free Radic Biol Med. 1997;22(1-2):359-78).

- ALA is included in a formulation as a lipid-soluble antioxidant to recycle Coenzyme Q10 from the pro-oxidant form to the antioxidant form. http://bit.ly/pU2ORy

- ALA also markedly increases intracellular glutathione (GSH), an abundant natural antioxidant and co-substrate for detoxification enzymes.

- Both ALA and DHLA chelate redox-active metals *in vitro* and *in vivo.* Thus, it helps the liver in detoxification pathways for heavy metal pollutants (Bustamante J et al., Free Radic Biol Med 1998 Apr;24(6):1023-39). (Shay et al., 2009; Biewenga et al., 1997; Randle, 1998).

- ALA has been implicated in processes of cell growth and differentiation (Bilska & Wlodek, 2005).

- NB! Because ALA only transiently accumulates *in vivo* and is rapidly catabolized, questions have been raised whether ALA could augment endogenous antioxidant capacity on sustained basis, although there is strong *in vitro* evidence for effects of ALA / DHLA as potent antioxidants. A paper by Carlson et al.(2008) argues that the transitional nature of ALA action is integral to its mechanisms of action and helps to ensure its safety.
- Nonetheless, there is growing evidence for indirect effects of ALA to maintain cellular antioxidant status; e.g. ALA increases intracellular vitamin C levels by inducing uptake from the blood plasma.

(Shay et al., 2009).

A claim on ALA and protection of body lipids from oxidative damage has not been substantiated by EFSA (EFSA opinion, 2010; EFSA opinion, 2011).

Annex 3: interactions

Common medications checked in combination with alpha-lipoic acid

- Aspirin Low Strength (aspirin)
- Calcium 600 D (calcium/vitamin d)
- Coenzyme Q10 (ubiquinone)
- CoQ10 (ubiquinone)
- Cymbalta (duloxetine)
- DHEA (dehydroepiandrosterone)
- EPA Fish Oil (omega-3 polyunsaturated fatty acids)
- Fish Oil (omega-3 polyunsaturated fatty acids)
- Ginkgo Biloba (ginkgo)
- L-Arginine (arginine)
- L-Carnitine (levocarnitine)
- Lipitor (atorvastatin)
- Lovaza (omega-3 polyunsaturated fatty acids)
- Omega 3-6-9 Complex (omega-3 polyunsaturated fatty acids)
- Plavix (clopidogrel)
- Vitamin B12 (cyanocobalamin)
- Vitamin B6 (pyridoxine)
- Vitamin C (ascorbic acid)
- Vitamin D2 (ergocalciferol)
- Vitamin D3 (cholecalciferol)

http://www.drugs.com/drug-interactions/alpha-lipoic-acid.html

http://www.shopping4net.com/no/Helsekost/Pleie-hygiene/Ansiktspleie/Oeyecremer/Jabu-she-eye-lift-serum.htm

Bing image search: alpha lipoic acid
Hits: 49400
http://www.bing.com/images/search?q=alpha+lipoic+acid&go=&form=QBLH&filt=all

A double-blind placebo-controlled study by Beitner (2003) demonstrated that 12 weeks of treatment with a cream containing 5% ALA resulted in improved clinical characteristics related to photoaging (i.e. skin damage caused by long-term exposure to the sun) of facial skin. The capability of ALA to reduce the number of fine wrinkles is also shared by alpha-hydroxy acids, vitamin C, and retinoid creams.
http://dermnetnz.org/site-age-specific/ageing.html