

Glucotize[®]

controlled-release α -lipoic acid

***An Oxidative Stress 'Antagonist'
that Enhances Glucose Metabolism***

Product Reference Guide



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Section 1

Glucotize

Product Reference Guide

1.1 Glucotize[®] Product Summary

Glucotize is a proprietary, orally active, controlled-release formulation of racemic α -lipoic acid, marketed to be a dietary supplement, manufactured by Medical Research Institute (MRI), San Francisco, CA. α -Lipoic acid is a disulfide compound that is produced in trace quantities in cells, where it functions naturally as a coenzyme in the pyruvate dehydrogenase and α -ketoglutarate dehydrogenase mitochondrial enzyme complexes. These enzymes are important for oxidative glucose metabolism.

α -Lipoic acid functions as a multi-functional antioxidant. Supplementation with α -lipoic acid provides a number of beneficial physiological effects:

1. Principal among these are improvements in the markers of oxidative stress such as increased tissue glutathione levels, reduced levels of lipid peroxides, and other markers of oxidative stress. This is significant because oxidative stress is associated with neurodegenerative diseases such as neuropathy.
2. Regeneration of the endogenous antioxidant network (including vitamins C and E).
3. Several clinical studies point to the beneficial effect α -lipoic acid has on whole-body glucose metabolism. (56)
4. Glucotize is also an ideal antioxidant to counteract the increased levels of free radicals generated during moderate to strenuous exercise.

The primary advantage of the Glucotize formulation is that it increases the length of time in plasma of α -lipoic acid (several hours). This provides Glucotize with a pharmacokinetic advantage that is a marked improvement over other α -lipoic acid products in which α -lipoic acid is rapidly cleared, usually within 30 minutes (2). Controlled-release technology is what makes Glucotize appropriate for use as a potent oxidative stress antagonist. Oxidative stress, and specifically its imbalance with antioxidant depletion, is associated neuropathy.

Controlled-release technology is also what improves the efficacy of α -lipoic acid in helping to control blood sugar levels. Data from a 12-week clinical study in patients with type 2 diabetes indicate that supplementation with Glucotize (1200 mg per day, divided doses as add-on therapy with other anti-hyperglycemic medications) demonstrated a number of benefits including a significant reduction of plasma fructosamine, along with a trend towards reduced C-peptide (3). The ability of α -lipoic acid to improve glycemic control when administered in a controlled-release formulation has not been reported previously with commercially available non-controlled release α -lipoic products. In addition, many subjects in the study exhibited a marked increase in insulin sensitivity (judged by a reduction in C-peptide). Whether taken alone, or in combination with other anti-hyperglycemic medications, Glucotize is well tolerated and does not produce alterations in liver or kidney function.

Glucotize, in summary, represents a scientifically developed and clinically tested dietary supplement for use as a multi-functional antioxidant to counteract free radical formation and to help promote healthy blood sugar levels. Most notably, Glucotize is appropriate as an adjunctive approach to reduce oxidative stress that has been linked to neuropathy.

1.2 Product Description

Glucotize is a controlled-release formulation of racemic α -lipoic acid. α -Lipoic acid is a disulfide compound that is produced in trace quantities in cells, where it functions naturally as a coenzyme in the pyruvate dehydrogenase and α -ketoglutarate dehydrogenase mitochondrial enzyme complexes. In effective doses, α -lipoic acid functions as a multifunctional antioxidant.

The primary advantage of the Glucotize formulation is that it increases the length of time effective concentrations of α -lipoic acid are present in plasma over time (several hours) (2). This provides Glucotize with a pharmacokinetic advantage that is a marked improvement over other α -lipoic acid products in which α -lipoic acid is rapidly cleared in 30 minutes. Glucotize represents a scientifically developed and clinically tested dietary supplement appropriate for use by individuals who are more susceptible to oxidative stress. Glucotize is an aid to enhance blood sugar metabolism. It is also for use as a multi-functional antioxidant in healthy individuals to counteract the increase in free radical formation during exercise.

1.3 Indications and Usage

Glucotize antagonizes oxidative stress and facilitates whole-body glucose utilization. In healthy individuals, Glucotize is indicated for the routine maintenance and enhancement of tissue and whole-body antioxidant status including increasing glutathione (the major intracellular antioxidant), vitamins C, and vitamin E. Also for healthy individuals, Glucotize is an ideal antioxidant to counteract the increased levels of free radicals generated during moderate to strenuous exercise.

Glucotize is an appropriate adjunctive approach for reducing the oxidative stress that has been associated with the symptoms of neuropathy. Similarly,

Glucotize, through its controlled-release technology, has exhibited positive effects on promoting healthy blood sugar levels.

In other conditions associated with high levels of oxidative stress, Glucotize should also be used as an approach to counteract the deterioration of mitochondrial function that occurs with aging.

1.3.1 Oxidative Stress and Neuropathy

Neuropathy has been causally linked to oxidative stress. There is considerable evidence to indicate that oxidative stress plays an important role in the etiology of diabetic complications. Many of the biochemical pathways (e.g. protein glycation, polyol pathway, and glucose oxidation) associated with hyperglycemia can result in increased free radical production.

1.3.2 Enhancing Blood Sugar Control

Glucotize is an appropriate adjunctive approach to enhance blood sugar control. α -Lipoic acid has been shown, through IV, to significantly increase insulin sensitivity in type 2 diabetics (as judged by % change in metabolic clearance rate). In contrast, oral administration of non-controlled-release tablets exerts a minimal effect on insulin sensitivity. (1)

Similarly, α -lipoic acid has exhibited positive effects on insulin sensitivity. Data from a 12-week clinical study in patients with type 2 diabetes indicate that supplementation with α -lipoic acid (1200 mg per day, divided doses as add-on therapy with other anti-hyperglycemic medications) demonstrated a number of benefits including a significant reduction of plasma fructosamine, along with a trend toward reduced C-peptide. (3)

In another study, subjects were given 1000 mg of α -lipoic acid daily. Metabolic clearance rate (MCR) increased 55% ($p < 0.05$) and insulin sensitivity increased 57% ($p < 0.05$). (1) Subsequently, the same group reported that dosages of 500 mg per day, for 10 days, enhanced MCR and insulin sensitivity by 30% ($p < 0.05$).

1.4 Contraindications, Precautions, and Adverse Reactions

Glucotize (and any product containing α -lipoic acid) is contraindicated in individuals with known hypersensitivity to α -lipoic acid, or other sulfur-containing compounds. Glucotize is contraindicated in individuals that are thiamin-deficient.

There is no evidence to suggest carcinogenic or teratogenic effects of α -lipoic acid. However, because of the lack of long-term safety data, any product containing α -lipoic acid should be avoided by women who are pregnant or lactating. It is prudent that any group likely to be severely thiamine-deficient (e.g. alcoholics) should receive supplemental thiamine if α -lipoic acid is given (4).

To date, α -lipoic acid in daily doses of 600-1800 mg have been well-tolerated. In humans, reported side effects include allergic skin reactions, and possible moderate hypoglycemia in diabetic patients, as a consequence of improved glucose utilization with very high doses (> 2000 mg per day). This dose is well above the dose recommended by MRI (see below). Nevertheless, those with diabetes and problems with glucose intolerance should monitor their blood glucose and adjust their anti-diabetic medication, if necessary, to avoid possible hypoglycemia.

1.5 Interactions

There are no known drug interactions with α -lipoic acid or with Glucotize. However, due to the ability of Glucotize to lower blood glucose levels, those with diabetes on anti-diabetic medication should monitor their blood glucose regularly and adjust the dose of their anti-diabetic medication, if necessary, to avoid possible hypoglycemia. A recent study has found that co-administration of single oral doses of non-controlled-release α -lipoic acid and glibenclamide, or non-controlled-release α -lipoic acid and acarbose did not result in drug-drug interactions (5).

1.6 Overdosage

There are no reports of α -lipoic acid over dosage.

1.7 Toxicity

At the recommended doses, α -lipoic acid is safe and well tolerated in humans (6). Published clinical studies indicate that doses up to 1800 mg/day are well tolerated (7). Neither animal nor human studies to date have reported significant side effects with the administration of α -lipoic acid. In rats, the LD50 is approximately 180 mg/kg following intravenous administration, and 1,130 mg/kg after oral dosing (8,9). The LD50 is 400-500 mg/kg after oral dosing in dogs (10). In long-term oral supplementation at doses sufficient to reduce body weight gain, no functional or laboratory adverse effects were observed in animals. A review of the safety and toxicology of α -lipoic acid prepared by an independent toxicologist is available from MRI.

1.8 Clinical Safety

In studies sponsored by MRI, Glucotize was evaluated (oral administration) at doses of 600, 900, and 1200 mg. At these doses, Glucotize was well tolerated with no significant treatment-related adverse events (see below and (3)). There were no clinically significant adverse effects with regard to vital signs or laboratory results, including those used to monitor and assess kidney and liver functions. The longest study of Glucotize was conducted for twelve weeks. At the recommended doses (600-1800 mg per day), α -lipoic acid is very well tolerated in humans (6). Human studies to date have reported no significant side effects with the administration of α -lipoic acid.

1.9 Pharmacokinetics

The pharmacokinetic parameters of α -lipoic acid delivered in Glucotize administered orally as a single 600 mg dose to healthy subjects have been evaluated (3). Glucotize possesses an approximate 2.5-fold increase in Tmax (time to maximum plasma concentration) compared to non-controlled-release α -lipoic acid. This results in an extended amount of time that therapeutic levels (i.e. μ M) of α -lipoic acid are maintained.

1.10 Metabolism (Excerpted From (8))

α -Lipoic acid can be reduced enzymatically and non-enzymatically to the dithiol, dihydrolipoic acid (DHLLA). This reduced form of the molecule greatly contributes to the antioxidant activity of α -lipoic acid in vivo. Another metabolic event of α -lipoic acid is the β -oxidation of its pentanoic side-chain. The principal metabolites that have been identified include 2-unsaturated lipoic acid, 3-methoxylipoic acid, 3-ketolipoic acid, and bisnorlipoic acid. In human plasma, the

maximum concentration of bisnorlipoic acid (704 ng/ml) was observed approximately 190 minutes after oral administration of 1 g of R-lipoic acid to a male subject. In urine, the main metabolite was S4,S6-dimethylbisnorlipoic acid, indicating that β -oxidation products are further metabolized before they are excreted in the urine. In conclusion, DHLA, bisnorlipoic acid, β -hydroxybisnorlipoic acid, and tetranorlipoic acid might contribute to the antioxidant effects of lipoic acid in vivo. The antioxidant properties of DHLA have been studied extensively and are well-established (8,10). Studies describing the antioxidant properties of bisnor- and tetranorlipoic acid are limited, and no information is available regarding the other metabolites.

1.11 Glucotize Clinical Trials

11.1.1 Pharmacokinetics

A single-dose pharmacokinetic study of Glucotize in healthy individuals has been completed. This study found that Glucotize maintains the effective plasma level of α -lipoic acid for an extended period of time (about three hours).

11.1.2 Safety, Tolerability, Efficacy

MRI has evaluated the tolerability, efficacy and pharmacokinetics of Glucotize in humans. An IRB-approved study of the effects of Glucotize on type 2 diabetics has been completed. Patients received 12 weeks of active treatment (900 mg/day for 6 weeks and 1200 mg/day for 6 weeks), and were monitored on a regular basis for glucose and lipid control, liver enzymes, along with other clinical markers. In this study, there were no significant side effects reported.

Importantly, there were no significant changes in liver enzymes, or liver or kidney

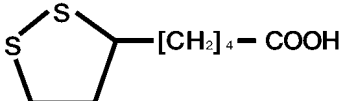
function (3). With regard to efficacy, a clinically beneficial effect ($p < 0.05$) with regard to the reduction of plasma fructosamine, an intermediate-term (~3-week) indicator of glucose control, was reported. In addition to the reduction in plasma fructosamine, a reduction in glycated hemoglobin (HbA1c) in about 50% of the subjects was observed. In this open-label study, all subjects remained on their existing anti-hyperglycemic medications; Glucotize was administered in combination with these other medications.

1.12 Glucotize Manufacturing

MRI purchases α -lipoic acid used in Glucotize from the world's largest supplier. This material is of the highest purity available, and manufactured under the equivalent of US FDA current Good Manufacturing Practices. MRI has devoted extensive resources to develop a controlled-release formulation of α -lipoic acid. Glucotize is the first and only commercially available controlled-release formulation of α -lipoic acid that has been evaluated clinically. It took well over 100 different formulations and experiments to achieve the steady state plasma levels resulting in therapeutic efficacy.

1.13 Chemistry

Chemical Name: α -lipoic acid; DL-thioctic acid; 1,2-dithiolane-3-pentanoic acid

Chemical Structure: 

Racemic mix: (~50:50 each enantiomer)

Molecular Weight: 206.3 (oxidized form)

Yellow crystalline solid

Melting point: ~62° C (racemic); ~42° C (individual enantiomers)

CAS Number: 1077-28-7

1.14 Glucotize Formulation

The formulation of Glucotize is designed to deliver α -lipoic acid in a controlled manner over a period of about 2-3 hours (3). The make-up of the formulation is proprietary and 3 US patents have been awarded (US Patent # 6,191,162 and 6,197,340(B1), and 6, 572,888(B2)).

1.15 Mechanism of Action

As is the case for many therapeutic agents, the molecular mechanism of action of α -lipoic acid is not known. There is evidence indicating that α -lipoic acid blocks the activation of NF- κ B, a redox sensitive and stress-activated transcription factor (11-14). However, it is not certain if this effect is linked to its physiological effects. α -Lipoic acid is a very potent antioxidant; it is able to regenerate Vitamins C and E, along with elevating glutathione levels. α -Lipoic

acid also forms stable complexes (chelates) with copper, manganese, and zinc (8,10) α -Lipoic acid functions essentially as an 'oxidative stress antagonist'. In this context, α -lipoic acid serves to counteract the damage to lipids, proteins, and DNA brought about by increased levels of free radicals. In individuals with type 2 diabetics, α -lipoic acid enhances glucose disposal and increases insulin sensitivity (7,15-17). In contrast to the new chemical class of anti-hyperglycemic medications (thiazolidinediones) that achieve this effect by acting as agonists to the nuclear hormone receptor PPAR γ (18), the mechanism by which α -lipoic acid increases insulin sensitivity is unknown but might involve the reduction of oxidative stress (11,19,20).

1.16 Dosage and Administration

As is the case with many supplemental regimes, dosing management should be individualized. For example, to protect against free radical accumulation, to improve tissue and whole-body antioxidant status, and to improve mitochondrial function, healthy individuals should take Glucotize daily (one tablet (300 mg) before breakfast and one tablet (300 mg) before dinner).

In individuals where free radical production is above normal, it is suggested to take two tablets (600 mg) before breakfast and one tablet (300 mg) before dinner.

In all cases, it is highly recommended to take Glucotize 30-60 minutes before eating, as absorption of α -lipoic acid might be affected (i.e. reduced) by food or delayed gastric emptying (21,22).

1.17 How Supplied

Glucotize is a dietary supplement product marketed in the US under the 1994 Dietary Supplement Health and Education Act (DSHEA). Glucotize is offered as an uncoated 300 mg tablet (racemic α -lipoic acid), and can be purchased directly from MRI. Glucotize is available in child-resistant plastic bottles containing 120 tablets.