

# Nerve Support SAP

Science-based formulation for nerve health

Peripheral nerves make up an intricate network that connect the brain and spinal cord to the muscles, skin, and internal organs. Diffuse damage to the peripheral nerve fibres results in peripheral neuropathy and diabetes is the commonest cause of painful peripheral neuropathy. The symptoms of peripheral neuropathy are debilitating and significantly affect the quality of life and impair physical and psychological functioning. In addition, mitochondria are subject to extensive oxidative damage, arising from nutrient deficiencies and environmental toxins. Mitochondrial dysfunction has been implicated in diabetes and neurological disorders.

**Nerve Support SAP** is a synergistic formulation targeted towards supporting healthy nerve function. **Nerve Support SAP** contains a combination of high quality active ingredients namely benfotiamine, N-acetyl-L-Carnitine, *R-alpha*-lipoic acid, methylcobalamin, and vitamin B<sub>6</sub> (pyridoxal 5-phosphate) for optimal nerve support. **Nerve Support SAP** helps improve overall peripheral nerve function. **Nerve Support SAP** helps improve symptoms associated with diabetic peripheral neuropathy and helps ameliorate mitochondrial abnormalities.

## ACTIVE INGREDIENTS

Each vegetable capsule contains:

Acetyl-L-Carnitine hydrochloride.....	500 mg
Benfotiamine (providing 85.5 mg of Vitamin B <sub>1</sub> ).....	150 mg
<i>R-alpha</i> -lipoic acid .....	100 mg
Vitamin B <sub>12</sub> (Methylcobalamin).....	333 mcg
Vitamin B <sub>6</sub> (pyridoxal 5-phosphate).....	16.67 mg

**Other ingredients:** Vegetable magnesium stearate and silicon dioxide in a vegetable capsule composed of vegetable carbohydrate gum and purified water.

**Contains no:** Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.

**This product is non-GMO and vegan friendly.**

**Nerve Support SAP** contains 90 capsules per bottle.

## DIRECTIONS FOR USE

**Adults:** Take 1 capsule three times daily or as directed by your healthcare practitioner. Consult a healthcare practitioner for use beyond 6 months.

## INDICATIONS

**Nerve Support SAP:**

- Helps improve overall peripheral nerve function.
- May help improve symptoms associated with diabetic peripheral neuropathy.
- Can help ameliorate mitochondrial abnormalities.
- Can help ameliorate mitochondrial dysfunction due to oxidative stress.

## CAUTIONS AND WARNINGS

Consult a healthcare practitioner prior to use if you are pregnant or breast-feeding; if you have liver disease, kidney disease, and/or seizure disorder; or if you have diabetes. Consult a healthcare practitioner if symptoms persist or worsen.

## PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for each **Nerve Support SAP** lot number have been tested by an ISO 17025 accredited third-party laboratory for identity, potency, and purity.



Scientific Advisory Panel (SAP):  
adding nutraceutical research  
to achieve optimum health



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## PERIPHERAL NEUROPATHY

The brain and spinal cord are connected to the muscles, skin, and internal organs through an intricate network made up of peripheral nerves. Diffuse damage to the peripheral nerve fibres is a typical characteristic of peripheral neuropathy. Diabetes remains the commonest cause of peripheral neuropathy, and 30–90% of patients with diabetes have painful diabetic peripheral neuropathy (DPN), with the highest prevalence in diabetic women.<sup>[1, 2]</sup> The symptoms are often debilitating including burning, tingling, electric shock-like sensations which negatively affect the quality of life and impair physical and psychological functioning, leading to anxiety and sleep disturbances.<sup>[2]</sup> The precise triggering factor of DPN remains elusive, however increased glycemic instability such as 'insulin neuritis', resulting in epineurial shunting, reduced intra-epidermal nerve fibre density, increased thalamic blood flow and autonomic dysfunction have been linked with DPN.<sup>[3]</sup>

## OXIDATIVE STRESS AND MITOCHONDRIAL DAMAGE IN DIABETIC NEUROPATHY

Nutrient deficiencies, environmental toxins, and oxidative damage affect the normal functioning of mitochondria, often referred to as the "powerhouse of the cell" which are complex cell organelles crucial for cell survival and death. The mitochondrial respiratory chain is also a powerful source of reactive oxygen species (ROS), primarily the superoxide radical and hydrogen peroxide. Particularly, mitochondrial DNA (mtDNA) is extremely sensitive to ROS damage due its close proximity to the region of ROS production.<sup>[4, 5]</sup> Mitochondria therefore become both the important sources and targets of oxidative damage.<sup>[4, 5]</sup>

## MITOCHONDRIA DYSFUNCTION IN NEURODEGENERATION

Mitochondrial dysfunction has been implicated in diabetes and neurological disorders.<sup>[6]</sup> The strong relation between mitochondrial dysfunction and neurodegeneration is explained by the fact that the brain uses 70% of ATP.<sup>[7]</sup> In neuronal cells, mitochondria accumulate predominantly at high energy demanding sites such as presynaptic terminals, nodes of Ranvier and active growth cones and branches.<sup>[6]</sup>

## NUTRACEUTICALS FOR NERVE SUPPORT:

### BENFOTIAMINE

Benfotiamine is a lipid-soluble precursor of thiamine with better bioavailability than thiamine and has been known to alleviate the severity of diabetic complications such as neuropathy, nephropathy and retinopathy.<sup>[3, 8]</sup> In the case of diabetes, benfotiamine blocks three of the major molecular pathways leading to hyperglycemic damage by increasing transketolase activity, a key enzyme in glucose metabolism.<sup>[8]</sup> Benfotiamine has been shown to prevent increases in UDP-N-acetylglucosamine (UDP-GlcNAc) and enhances hexosamine pathway activity, thereby inhibiting the formation of advanced glycation end products (AGEs).<sup>[8]</sup> Benfotiamine is absorbed via passive diffusion through the intestinal mucosa and is rapidly converted to biologically active thiamine. In experimental animal models, benfotiamine has been shown to improve cardiomyocyte contractile dysfunction, reduce neuropathic pain and improve post-ischemic healing. Moreover, benfotiamine has been shown to reduce oxidative stress in a mechanism unrelated to its anti-AGE property.<sup>[3, 8]</sup>

In a double-blind, randomized, placebo-controlled pilot study, 40 subjects with diabetic polyneuropathy received two 50 mg tablets benfotiamine four times daily (400 mg total daily dose) or placebo for 3 weeks. Benfotiamine supplementation significantly improved neuropathy score with decrease in pain compared to placebo.<sup>[9]</sup> In another study that investigated the effect of benfotiamine in combination with other B vitamins (400 mg benfotiamine and 2,000 µg cyanocobalamin for three weeks) in 45 patients with painful peripheral polyneuropathy, profound relief in neuropathic pain and improvement in vibration perception thresholds were observed compared to the conventional B-vitamin treatment.<sup>[10]</sup> Similar results were observed in other clinical studies investigating the effects of benfotiamine in the treatment of DPN.<sup>[11, 12]</sup>

### N-ACETYL-L-CARNITINE:

Acetylcarntine (ALC) is a derivative of L-Carnitine which is a conditionally essential amino acid crucial for transporting long-chain fatty acids across the inner mitochondrial membrane for the process of beta-oxidation. ALC is better absorbed and more efficiently transported than L-Carnitine.<sup>[13]</sup>

ALC has been suggested to support healing of damaged neurons. Especially, in an animal model study, ALC supplementation induced regrowth of the nerve cells in animals that underwent a nerve division followed by nerve repair.<sup>[14]</sup> Carnitine supplementation has been suggested to improve the damaged and retrograde transport within nerve cells usually observed in the case of DPN.<sup>[15]</sup> ALC has also been found to upregulate the mGlu2 metabotropic glutamate receptor that induces analgesia in certain parts of the brain.<sup>[16]</sup>

ALC supplementation significantly reverses the age-associated decline of mitochondrial membrane potential.<sup>[13]</sup> ALC supplementation can ameliorate oxidative mitochondrial decay, a major contributor to aging. Co-administration of ALC with ALA has been reported to improve mitochondrial abnormalities.<sup>[17]</sup>

In a multicenter, long term clinical study, ALC supplementation of 2000 mg/day for 12 months significantly improved neurophysiological parameters in reducing pain associated with diabetic neuropathy compared to the placebo and was well tolerated.<sup>[18]</sup> A meta-analysis of clinical studies comparing the efficacy and safety of ALC for the treatment of patients with peripheral neuropathic pain showed that ALC has a moderate effect in reducing pain in PNP patients with acceptable safety.<sup>[19]</sup>

### R-ALPHA-LIPOIC ACID:

Alpha-lipoic acid (ALA) is an endogenous disulfide compound synthesized *de novo* in mitochondria. Apart from its well-established role in mitochondrial energy metabolism and antioxidant effects, various studies have shown that ALA also exerts other beneficial effects including attenuation of mitochondrial decay during aging and mitochondrial targeted anti-tumor effect.<sup>[20]</sup> Maximal absorption and plasma concentration levels are ~50% higher for the R-isomer (naturally synthesized and used in biological systems) versus the S-isomer of ALA.<sup>[21]</sup> ALA is also extensively recommended for treatment of diabetic neuropathy.<sup>[22]</sup> ALA treatment for 24 h improved insulin sensitivity, restored expression levels of mitochondrial OXPHOS complexes and increased intracellular ATP production in an endoplasmic reticulum stress cell model.<sup>[22]</sup> In addition, ALA enhanced the  $\beta$ -oxidation capacity of the mitochondria

and abated oligomycin-induced mitochondrial dysfunction.<sup>[23]</sup>

In a meta-analysis of four placebo-controlled trials it was found that administration of 600 mg/day of ALA over 3 weeks resulted in a clinically meaningful improvement in the symptoms of DPN.<sup>[21, 24]</sup>

### VITAMIN B<sub>12</sub> (METHYLCOBALAMIN)

Methylcobalamin acts as a cofactor in myelin synthesis; synthesis of neurotransmitters, such as serotonin, dopamine, and norepinephrine and the methylation of the toxic byproduct homocysteine, known to negatively affect neurons.<sup>[25]</sup> Methylcobalamin is therefore very crucial for the maintenance of a healthy nervous system and any deficiency usually affects the brain, spinal cord, the peripheral and the optical nervous system.<sup>[26, 27]</sup> Adequate intake is necessary for promoting normal reflexes, vibration sense, motor neuron function and improving sensitivity to pain.<sup>[26, 27]</sup> Methylcobalamin supplementation imparts a balancing effect on sympathetic and parasympathetic nervous systems and regulates heart rate variability.<sup>[28]</sup> Hypomethylation in the central nervous system can contribute to vitamin B<sub>12</sub> deficiency-related neuropathy, specifically diabetic neuropathy.<sup>[29]</sup> Methylcobalamin has been suggested to promote injured nerve and axonal regeneration and negate glutamate-induced neurotoxicity.<sup>[29]</sup> In an open-labeled, single arm, observational clinical study, patients who received a fixed dose of combination of 75 or 150 mg sustained-release pregabalin combined with 1500 µg immediate release methylcobalamin experienced significant reductions in neuropathic pain along with substantial improvement of neuropathy associated symptoms.<sup>[30]</sup>

### VITAMIN B<sub>6</sub>

Vitamin B<sub>6</sub> is a highly water-soluble vitamin that is required for the proper functioning of over 140 enzymes involved in amino acid, fatty acid, and homocysteine metabolism, as well as in glycogen degradation, DNA/ RNA synthesis, gene expression, and hemoglobin formation.<sup>[31, 32]</sup> It is required in the synthesis of several neurotransmitters including the conversions of DOPA to dopamine, tryptophan to serotonin, and glutamic acid to  $\gamma$ -aminobutyric acid (GABA).<sup>[32, 33]</sup>

Deficiency may also produce peripheral neuropathy, which is, ironically, one of the main symptoms associated with B<sub>6</sub> toxicity.<sup>[34]</sup> In addition, four inborn errors of B<sub>6</sub> metabolism have been identified that cause early-onset, drug-refractory, convulsive seizures,<sup>[35]</sup> possibly due to decreased GABA synthesis.<sup>[33]</sup> Three of these conditions respond to supplementation of B<sub>6</sub> in any form, but patients suffering from a deficiency in the enzyme pyridox(am)ine phosphate oxidase require P5P specifically.<sup>[35]</sup>

Carpal tunnel syndrome (CTS) is a common condition believed to be caused by compression of the median nerve as it passes through the carpal tunnel.<sup>[36]</sup> Vitamin B<sub>6</sub> is a critical cofactor in the synthesis of neuronal proteins, and is involved in numerous other pathways that affect peripheral nerve function, including neurotransmitter synthesis, amino acid metabolism, and sphingolipid biosynthesis and degradation.<sup>[36]</sup> It also has the ability to act as an analgesic, possibly by up-regulating GABA and serotonin synthesis.<sup>[36]</sup> The literature shows symptomatic relief for some people at doses of up to 200 mg/d.<sup>[36]</sup> A gradual tapering of the dose after 3 months for patients who experience an improvement in their symptoms is recommended.<sup>[34]</sup>

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