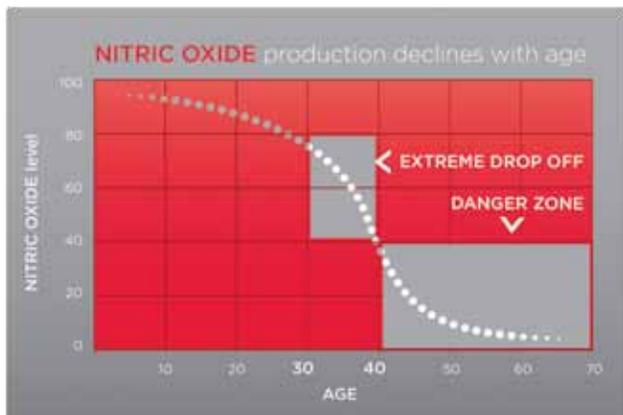


# PRIME nitric oxide **activator**

## CONCEPT

The new PRIME Nitric Oxide Activator is a cutting-edge nutritional supplement, nearly a decade of research investment. It is scientifically designed with a completely unique and improved method for restoring Nitric Oxide back to optimal levels in adult men and women.

Nitric Oxide is a gaseous molecule that plays a critical role in cell signaling, and has serious consequences on the health of the cardiovascular system and many other physiological processes. It's documented that the human body produces less Nitric Oxide with age; a typical 40-year-old adult creates approximately 50 percent less Nitric Oxide than a healthy 20-year-old. Scientific evidence suggests that increasing Nitric Oxide production may improve cardiovascular health by facilitating highly specific circulatory system processes, including vasodilation. The PRIME Nitric Oxide Activator contains several Nitric Oxide precursors, oral probiotics and other phytochemicals designed to improve and optimize endogenous Nitric Oxide production. PRIME also comes with a novel Instant Indicator that gives accurate measurements of total body Nitric Oxide availability based on a saliva sample. PRIME provides the tools needed to improve cardiovascular health and overall well-being.



## PUBLIC HEALTH RELEVANCE

Approximately 17.3 million people died from cardiovascular disease in 2008, according to the World Health Organization (WHO). Cardiovascular disease accounted for 30 percent of all deaths

worldwide. Rising levels of obesity, hypertension, type 2 diabetes, and other chronic illnesses are a growing public health concern. These chronic diseases are significant risk factors for later cardiovascular disease. The WHO estimates that cardiovascular disease will become the leading cause of death by 2030, contributing to 23.6 million deaths worldwide.

In addition to reducing longevity, cardiovascular disease causes significant public health burdens. Individuals with cardiovascular disease experience increased functional disability, utilize primary care and hospital resources more frequently, use more prescription medications, and often require rehabilitation services. In 2008, the total cost of cardiovascular disease and stroke in the United States was \$297.7 billion, according to a 2012 report from the American Heart Association.

Growing awareness of the serious medical and financial burden of cardiovascular health has generated interest in biological mechanisms and pharmaceutical interventions that can lower cardiovascular risk. Nitric Oxide (N-O), sometimes known as nitrogen monoxide has emerged as a compound of interest in improving overall cardiovascular functioning as well as benefiting other body systems. Nitric Oxide is a cell-signaling molecule that is implicated in a host of physiological processes including blood circulation, memory, cognitive functioning, neurotransmission, gastrointestinal processes, gene regulation and delivery of nutrients to cells. Because of the varied effects of N-O, dysregulation of the Nitric Oxide signaling pathway is implicated in several health conditions including memory and cognition disorders, sexual dysfunction, autoimmune disorders and nearly all cardiovascular risk factors.

Although N-O has a recognized role in a variety of physiological processes, it is perhaps best known as a molecule beneficial to cardiovascular health. In 1992, the American Association for the Advancement of Science proclaimed N-O the "Molecule of the Year" for its role as a biological messenger with beneficial effects on the cardiovascular system.

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N-O has been demonstrated to improve circulation, facilitate efficient delivery of oxygen and nutrients to cells, dilate arteries and support healthy blood pressure already within a normal range\*. The PRIME Nitric Oxide Activator facilitates natural N-O production pathways in the body by providing the best raw materials by which the body can synthesize Nitric Oxide. It does this by providing the body with several Nitric Oxide precursors and compounds proven to efficiently and effectively convert to N-O in the body. This product increases the body's natural production of this beneficial molecule.

Although scientists have found N-O to be a potent activator of circulatory processes, the general population remains uninformed of the potential benefits of this molecule. In a 2003 survey conducted by NFO Plog Research Inc., **researchers found that less than 1 percent of individuals correctly identified Nitric Oxide as a compound that benefits blood circulation.** Nearly one-fourth of respondents confused Nitric Oxide with laughing gas, or nitrous oxide. As scientific research about the benefits of Nitric Oxide continues to accumulate, it is important for scientists and health professionals to disseminate this crucial information to the public.

## DID YOU KNOW?

- *In 1998 a Nobel Prize in Medicine was awarded scientists for their discovery of Nitric Oxide as a cellular signaling molecule.*
- *Well over 100,000 scientific articles have been published about the effects of Nitric Oxide on cardiovascular health and other physiological processes.*
- *More than 200 government-approved Nitric Oxide clinical trials are currently underway.*
- *African-American populations have been shown to naturally produce less Nitric Oxide than people of other ethnicities.*
- *The average 40-year-old produces 50 percent less Nitric Oxide than he or she did at age 20.*
- *Declining N-O production causes hardened arteries, restricted circulation and plaque accumulation.*
- *Lower natural endothelial Nitric Oxide production is associated with future atherosclerotic disease progression.*

## A BRIEF HISTORY OF NITRIC OXIDE SCIENTIFIC RESEARCH

The physiological effects of Nitric Oxide were first recognized in 1876 by physician Thomas Lauder Brunton. Brunton experimented on a patient with angina by placing nitrite drops on a cloth for the patient to inhale. Within one minute, the patient's pulse improved, his face became flushed with blood and his pain subsided. Brunton concluded that the nitrite compound caused blood vessels to dilate, decreasing chest pain. However, he did not know the specific molecule that caused the effect nor its mechanism of action.

In the hundred years following Brunton's discovery, scientists further explored the effects of Nitric Oxide on the cardiovascular system. English pharmacologist Henry Dale performed several experiments on vasodilators in the early 1900s, including work with amyl nitrite, a biological source of Nitric Oxide. Dale found



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that amyl nitrite operates peripherally to dilate blood vessels without acting through the nervous system. Scientists did not identify Nitric Oxide as the messenger molecule or understand its action until the late 20th century.

In the mid-1970s, Albanian-American physician Ferid Murad demonstrated that nitrite-containing compounds stimulated soluble guanylate cyclase, an enzyme found in smooth muscle that increases cyclic guanosine monophosphate (cGMP) levels. Murad demonstrated that this rise in cGMP caused smooth muscle relaxation, dilating blood vessels. The researchers proposed that this smooth muscle relaxation occurred via the action of Nitric Oxide, although they did not experimentally demonstrate this association. In 1981, pharmacologist Louis J. Ignarro performed the experiments that identified Nitric Oxide as a gaseous messenger molecule capable of acting on smooth muscle and other types of cells. As a result of these experiments, Murad, Ignarro, and Robert F. Furchgott received the 1998 Nobel Prize in Physiology or Medicine. The Swedish Nobel committee commented that "The signal transmission by a gas that is produced by one cell, penetrates through membranes and regulates the function of another cell, represents an entirely new principle for signaling in biological systems." Before its identification as a molecule responsible for circulatory system improvement, Nitric Oxide was thought to be a waste byproduct of fossil fuel combustion and other chemical reactions.

The researchers who discovered Nitric Oxide and first explored its actions were hailed for their profound contribution to the understanding of cardiovascular health. In 1998, the then-president of the American Heart Association, Dr. Martha Hill, remarked that "the discovery of Nitric Oxide and its function is one of the most important in the history of cardiovascular medicine." Since the Nobel Prize award in 1998, thousands of scientific articles have further explored the association between Nitric Oxide activity and cardiovascular health.

## NITRIC OXIDE MECHANISMS OF PRODUCTION

### *L-Arginine N-O Production Pathway*

The most well known N-O pathway is the conversion of L-arginine to Nitric Oxide. The body naturally produces Nitric Oxide as an intermediate compound in the conversion of L-arginine, a semi-essential amino acid, to nitrite. L-arginine is commonly found in dietary sources of proteins including dairy products, beef, pork, poultry, nuts, and seeds. A class of enzymes called Nitric Oxide synthases (NOS) act on L-arginine, oxidizing one of its nitrogen molecules. The activity of NOS relies on the presence of six cofactors. Two types of NOS, endothelial NOS-3 and neuronal NOS-1, depend on calcium to oxidize L-arginine and generate Nitric Oxide. These enzyme isoforms produce relatively low levels of N-O, allowing the molecule to diffuse to nearby cells to exert its effects. The other NOS isoform, inducible NOS-2, creates Nitric Oxide through a calcium-independent process. NOS-2 produces larger amounts of Nitric Oxide than the calcium-dependent enzyme isoforms.

The N-O that is formed through the L-arginine reaction exists as a gaseous molecule that lasts only a few seconds. Nitric Oxide is highly reactive, meaning that it easily reacts with other molecules to form new compounds. The most prominent example of Nitric Oxide reactivity is the reaction of N-O with oxygen to form nitrogen dioxide. As a result of its reactivity, Nitric Oxide has the ability to act upon nearby cells but cannot travel long distances to act upon faraway physiological targets. This makes N-O ideally suited to act as a messenger with localized action between groups of related cells.

Many products on the market are entirely based on the conversion of L-arginine. An entire category of bodybuilding supplements are being marketed as Nitric Oxide producing, all using this pathway.

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However L-arginine supplements have significant limitations. Because this pathway is highly complex and has 6 required co-factors, very little L-arginine is actually converted into N-O. In fact there are at least 8 different pathways L-arginine can be used in, other than Nitric Oxide, so less than 3% of L-arginine is actually converted into N-O. Therefore, supplementation with L-arginine has serious limitations and studies show it can make many health conditions worse if it goes unconverted. This is especially true in patients with existing heart conditions and in people over the age of 60. In one notable study the researchers in the Journal of the American Medical Association concluded that L-arginine will probably only work in people with “preexisting L-arginine deficiency” (such as chronic kidney disease or people with elevated ADMA). They also noted that people over age 60 won’t experience any benefit as they undergo metabolic changes that make inhibit their use of the amino acid. Finally, they noted that without NOS cofactors guaranteeing production of N-O, L-arginine generates cell-damaging “reactive oxygen species.”

So while L-arginine can stimulate production of N-O and provide the benefits of N-O, supplements based entirely on L-arginine are limited in their efficacy and safety profile.

## **Alternate N-O Production Pathways**

In addition to Nitric Oxide production from the conversion of L-arginine, the body also creates N-O through a pathway independent of NOS activity. People receive nitrate and nitrite through dietary sources such as green leafy vegetables, certain root vegetables, meat products, and drinking water. Several strains of anaerobic bacteria in the tongue and in the gastrointestinal tract perform a reduction reaction that converts nitrate to nitrite. Human cells cannot effectively metabolize nitrate, meaning that the body relies on oral bacteria to perform this nitrate reduction function.

Approximately 25 percent of nitrate from dietary sources is secreted in saliva. Of that salivary nitrate, nearly 20 percent is converted to nitrite by these

oral probiotic bacterial strains. The result of this bacterial activity is a concentration of nitrite in the saliva; salivary nitrite levels are nearly 1,000 times higher than plasma nitrite levels.

As the saliva travels through the digestive system, it comes into contact with gastric acid in the stomach. Approximately 1 to 1.5 liters of saliva enter the stomach in this way every day. When nitrite comes into contact with stomach acid, it reacts to form nitrous acid, or HNO<sub>2</sub>. The gastric acid further reduces nitrous acid to form N-O. This reaction occurs independently of NOS, constituting a separate pathway of Nitric Oxide production. This N-O synthesis pathway depends on dietary intake of nitrate and nitrite, not the presence of L-arginine.

Although considerable Nitric Oxide production occurs in the reaction of nitrite with gastric acid, not all available nitrite is converted in this way. The gastrointestinal system absorbs excess nitrite, storing it in cells throughout the body. Once within the cells, nitrite can form Nitric Oxide through a reaction with a ferrous heme protein. However, this process does not produce N-O as efficiently as other pathways. The storage of nitrite within cells creates a reserve pool that the body can access to create more N-O molecules.

## **NITRIC OXIDE MECHANISMS OF ACTION**

### ***cGMP-Mediated Pathways***

Once created through NOS-dependent pathways or the nitrate/nitrite conversion pathway, Nitric Oxide acts on its physiological targets through several mechanisms. A primary mechanism of N-O action is through cGMP-dependent signaling. Soluble guanylyl cyclase, or sGC, is directly activated by Nitric Oxide. In turn, sGC activates cyclic guanosine monophosphate, or cGMP. This important signaling molecule acts upon a variety of physiological targets, including cells in the cardiovascular, nervous and digestive systems. For example, Nitric Oxide in endothelial cells of blood vessels diffuses into the blood cell lumen to

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activate smooth muscle receptors. These receptors trigger a cascade of events resulting in a decrease in intracellular calcium levels. This change in calcium causes smooth muscle relaxation, increasing blood vessel diameter and facilitating blood flow. Nitric Oxide also acts upon neurons, cells in the gastrointestinal system, and other tissue types through similar cGMP-mediated processes.

### ***S-nitrosothiol (RSNO)-Mediated Pathways***

Nitric Oxide also works through a biological pathway independent of cGMP. A group of molecules called S-nitrosothiols (RSNOs) affect circulatory system activity and other physiological processes. These S-nitrosothiols act as carriers of Nitric Oxide, allowing it to affect other cellular systems. S-nitrosothiols activate ion channel proteins, proteolytic enzymes, gene transcription factors, and proteins involved in energy transduction. Nitric Oxide works through S-nitrosothiol activity to regulate programmed cell death, cell signaling, inflammatory responses and vascular tone. Many of these physiological processes cause the cardiovascular benefits for which N-O is best known.

### **PRIME NITRIC OXIDE ACTIVATOR FEATURES**

PRIME Nitric Oxide Activator is a nutritional supplement that enhances endogenous Nitric Oxide production. The supplement contains a blend of natural ingredients that provide the body with

nitrate and nitrite, precursor compounds required for Nitric Oxide production. After taking the supplement, individuals experience an increase in systemic Nitric Oxide availability, meaning that their bodies have the molecules necessary to produce N-O naturally. Unlike other available Nitric Oxide supplements, PRIME Nitric Oxide Activator provides multiple sources of N-O precursors that the body can utilize, rather than relying solely upon L-arginine as a source of N-O synthesis.

Significant research, method development and quantitative testing went into selecting the ingredients most likely to have the best ability to convert to N-O in the most efficient manner. For the first time, PRIME researchers developed a new method for testing and quantifying the N-O potential of different organic substances. A new algorithm was created to measure the Nitric Oxide potential of hundreds of foods, roots, plants, leaves, extracts, herbs and botanicals. Each was measured and scored to determine its Nitric Oxide potential in humans. Only the top scoring N-O ingredients were selected, making PRIME the most reliable and efficient formula on the market for generating N-O. In addition to nitrates, other cofactors were also included in the formula to ensure the most effectual conversion ratios.

PRIME also contains L-citrulline, which converts to L-arginine in the body. Researchers have suggested and reported that L-arginine made from L-citrulline is much more effective at raising N-O levels than taking L-arginine directly. This is because while L-arginine can travel down one of eight pathways, L-citrulline



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converted to L-arginine is directed toward the Nitric Oxide pathway, make L-citrulline much more efficient at fueling N-O.

PRIME Nitric Oxide Activator also contains the ProBiora3<sup>®</sup> Oral Probiotic Blend, a proprietary formula of beneficial bacteria. Each dose of PRIME contains 600 million colony-forming units of *Streptococcus oralis*, *S. uberis* and *S. rattus*. These healthy bacteria proliferate in the mouth, fostering an environment that facilitates N-O production. Without a strong population of probiotic bacterial strains in the mouth, an individual would be unable to efficiently produce Nitric Oxide.

## FREQUENTLY ASKED QUESTIONS

### What are the benefits of using PRIME Nitric Oxide Activator?

The PRIME Nitric Oxide Activator contains a proprietary blend of natural ingredients proven to boost an individual's Nitric Oxide production. Having higher levels of available N-O in the body is beneficial to adults. The health benefits of increasing Nitric Oxide production through use of the PRIME supplement include:

- *Maintenance of healthy blood pressure levels.\**
- *Improvement in circulation by signaling arterial smooth muscle to relax, dilating blood vessels.\**
- *Prevention of premature cardiovascular aging by improving blood vessel health.\**
- *Improvement of sexual functioning by increasing blood flow to penile and vaginal tissues.\**
- *Support for neuronal communication, memory processes, and overall cognition.\**
- *Improvements in energy, mood, and general feelings of well-being.\**

These benefits of Nitric Oxide have been demonstrated by several scientific studies. Each of these benefits of the PRIME Nitric Oxide Activator is discussed in greater detail below:

- *Endothelial cells that form the lining of artery walls naturally produce N-O. Nitric Oxide diffuses from these endothelial cells to affect smooth muscle contractility. A steady release of Nitric Oxide from these cells maintains vascular tone, preventing arteries from becoming too tightly contracted or too relaxed. As individuals age, their natural production of N-O significantly decreases. One result of this lower basal N-O production is dysregulation of vascular tone, causing artery walls to become too constricted. Elevated vascular tone contributes to changes in blood pressure, a major risk factor for cardiovascular disease. Taking PRIME Nitric Oxide Activator stimulates natural N-O production in endothelial cells, causing arterial walls to relax. This dilates blood vessels, supporting normal blood pressure already within normal range and promoting overall cardiovascular health.*
- *Increased N-O production improves overall circulatory system activity. Arterial dilation promotes efficient blood flow through the circulatory system. This speeds delivery of oxygen and other nutrients to cells while facilitating the efficient removal of waste products. These circulatory system improvements are another key benefit of taking PRIME Nitric Oxide Activator.*
- *Increasing natural N-O production by taking the PRIME supplement also improves blood vessel health, preventing premature cardiovascular aging. Unhealthy blood vessels are characterized by inflammation, circulatory constriction, hardening of arteries, platelet aggregation and adhesion of leukocytes to arterial walls.*

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*Nitric Oxide diffuses from endothelial cells into the lumen of the blood vessels, allowing it to interact with platelets and leukocytes. N-O has an inhibitory effect on platelet aggregation, breaking apart existing aggregations and preventing formation of new platelet clumps. It also inhibits adhesion of leukocytes to blood vessel walls. These functions improve vascular endothelial integrity, keeping blood vessels free of blockages and improving cardiovascular health. Studies have demonstrated that increasing N-O production in endothelial cells supports healthy blood vessels by signaling relaxation and expansion, improving circulation, inhibiting platelet aggregation and returning them to normal, healthy function.*

- *Using PRIME Nitric Oxide Activator also supports normal sexual functioning. Eighty percent of sexual dysfunction is related to circulation. In males it occurs because of impaired blood flow to penile tissue, preventing the individual from achieving a full erection or sustaining his erection. Reduced blood flow to vaginal tissue may also be implicated in sexual dysfunction in women.*

*Because Nitric Oxide acts as a vasodilator, it improves blood flow to the penis. Commonly used interventions for dysfunction make use of the Nitric Oxide pathway to boost blood flow to the sex organs. PRIME Nitric Oxide Activator regulates Nitric Oxide levels through natural means, improving blood flow and sexual performance.*

- *In addition to its effects on the cardiovascular system, Nitric Oxide has been implicated in key nervous system processes. Nitric Oxide has been demonstrated to act as a neurotransmitter in the brain, facilitating healthy and normal communication between neurons. Because*

*the molecule can diffuse through cellular membranes, it is an ideal messenger for engaging multiple nearby neurons. N-O can even transmit a signal between two neurons unconnected by a synapse, giving it a greater ability to communicate than traditional neurotransmitters that are more spatially limited. Nitric Oxide's relatively short lifespan allows it to activate several neurons in close proximity without affecting neural networks in other areas.*

*Nitric Oxide affects cognitive performance through the action of cGMP, a second messenger that triggers a cascade of reactions that affect neural activity. The Nitric Oxide-cGMP cascade is involved in long term potentiation, a process by which two or more neurons become associated following synchronous activation. Long-term potentiation underlies learning and memory processes by allowing neurons to become linked in complex networks. N-O activity facilitates memory processes, maintenance of attention and the activity of other neural networks involved in cognition. Taking PRIME Nitric Oxide Activator increases Nitric Oxide production, enhancing cognitive abilities. In a 30-day clinical trial of the PRIME supplement, more than 50 percent of participants reported improvements in anxiety symptoms, indicating that the enhanced N-O production has significant effects on mental health and cognition.*

- *In the clinical research study of adults taking the PRIME supplement, more than half of the participants reported improvements in overall energy. Because Nitric Oxide facilitates circulatory processes, most people experience a boost in energy. Other common effects of PRIME include improved mood, enhanced sleep quality and better sustained energy levels.*

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## How does the PRIME Nitric Oxide Activator work to enhance N-O production?

The PRIME Nitric Oxide Activator makes use of a multi-pronged approach to enhance in vivo Nitric Oxide production. The central approach of the PRIME supplement is to make use of the natural physiological process by which the body converts nitrate and nitrite to Nitric Oxide. PRIME maximizes endogenous Nitric Oxide production by:

- *Increasing the availability of Nitric Oxide precursors. PRIME ingredients contain high levels of nitrate and nitrite, which the body converts into N-O. Excess nitrate and nitrite are stored in cells, creating a reserve pool that can be accessed to synthesize more Nitric Oxide when levels drop.*
- *Facilitating the conversion of nitrate into nitrite. Although the body naturally contains anaerobic bacteria in the oral cavity and gastrointestinal system, PRIME supplements these existing bacteria with 600 million colony-forming units of bacterial strains that are equipped to convert nitrate into nitrite. This increases the amount of nitrite available for synthesis of Nitric Oxide.*
- *Enhancing the efficiency of the conversion of nitrite to Nitric Oxide. PRIME contains ingredients that have high nitrite reductase activity, increasing the speed and efficiency with which N-O is created from available nitrite. This ensures that the body can quickly produce Nitric Oxide and maintain high levels over a sustained period of time.*

## What makes PRIME Nitric Oxide Activator unique?

Although there are several other Nitric Oxide supplements on the market, the PRIME Nitric Oxide Activator provides several benefits over its alternatives. The key differentiator of PRIME over existing supplements is that PRIME is the only supplement on the market to engage multiple pathways in the body to product Nitric Oxide, not just L-arginine.

Benefits of using the PRIME Nitric Oxide Activator include:

- *PRIME contains all-natural ingredients.*
- *The proprietary blend of ingredients is specially formulated to optimize N-O production and restore balanced levels of N-O.*
- *PRIME supplements nitrate levels rather than only providing L-arginine to stimulate N-O production.*
- *PRIME Nitric Oxide Activator contains special ingredients that boost nitrite reductase activity, enhancing conversion of nitrite into N-O.*
- *The product contains several strains of oral probiotics, required for the conversion of nitrate to nitrite.*
- *PRIME makes use of a novel N-O Instant Indicator, the first scientific measurement of total body Nitric Oxide availability.*



Unlike other N-O supplements and pharmacological interventions, PRIME Nitric Oxide Activator is the first product to contain a blend of natural ingredients, proven to produce N-O through all the body's systems known to produce Nitric Oxide. While PRIME does make efficient use of the L-arginine pathway with efficacious doses of L-citrulline (which converts to L-arginine to Nitric Oxide), PRIME employs much more efficient and effective pathways for generating Nitric Oxide.

Qivana partnered with leading Nitric Oxide researchers to investigate and quantify the N-O potential in hundreds of botanical ingredients and

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desiccated food products to determine which compounds contained the ideal amounts of Nitric Oxide precursors. PRIME contains a proprietary blend of ingredients that optimize endogenous Nitric Oxide production. Because natural Nitric Oxide production decreases with age, this blend of ingredients has a unique ability to replace N-O and restore balanced levels of the signaling molecule.

Most other Nitric Oxide supplements make use of the synthesis of N-O as an intermediate during the conversion of L-arginine to nitrite. This pathway is highly inefficient and requires megadoses of L-arginine daily (10-30 grams) to have an impact on N-O production. While there is no doubt Nitric Oxide can be affected by L-arginine supplementation, studies show that less than 3% of L-arginine is actually converted into Nitric Oxide. Additionally, this N-O production pathway depends on the action of NOS enzymes as well as six cofactors. In clinical trials, supplementation of L-arginine has consistently failed to optimize N-O levels and improve cardiovascular functioning. PRIME Nitric Oxide Activator is unique in that it targets the conversion of nitrate and nitrite to N-O. Converting nitrite to Nitric Oxide requires considerably less energy than the L-arginine pathway of N-O production. This makes PRIME an ideal N-O supplement, providing precursors to Nitric Oxide and allowing the body to sustain balanced levels of the molecule.

PRIME also differs from other supplements on the market because it includes a compound that improves the reaction that converts nitrite to Nitric Oxide. This reaction depends on a class of nitrite reductase enzymes. By including a compound with excellent nitrite reductase activity, PRIME simultaneously boosts nitrite availability and stimulates conversion of nitrite to Nitric Oxide. This blend of ingredients increases the efficiency of N-O synthesis and promotes the sustained production of the messenger molecule.

One primary reason that PRIME Nitric Oxide Activator improves efficiency of N-O production is the inclusion of oral probiotics in the supplement. With each PRIME dose containing 30 milligrams of ProBiora3<sup>®</sup> Nitric Oxide Probiotic Blend, the supplement populates the mouth and gastrointestinal system with three probiotic bacterial strains: *S. oralis*, *S. uberis* and *S. rattus*. These bacteria have been shown to enhance the conversion of nitrate into nitrite, significantly increasing nitrite availability. This probiotic blend allows the body to build up a reserve of nitrate and nitrite levels, making N-O precursor molecules constantly available for use.

## **What are indicators that PRIME is working?**

Several factors indicate that PRIME is restoring healthy Nitric Oxide levels and improving cardiovascular health. Common effects include sharper mental acuity, greater sleep quality, boosted mood, improvements in energy levels and overall feelings of well-being. Checking the body's N-O levels with the N-O Instant Indicator provides an accurate measurement of how well PRIME is working.

## **How long does it take to see results?**

The length of time it takes to experience changes after taking PRIME depends on individual biochemistry and personal health variables. Some people experience improved mood and feelings of well-being after just three days. It is generally recommended that individuals begin by taking 2 packets per day, 12 hours apart, for the first 30-60 days. This initial phase acts as a loading phase. After a 30-60 day loading phase, most individuals can maintain optimal levels of N-O by taking a single packet per day. However, each individual will see different results, and should gauge their N-O health using the N-O Instant Indicator to monitor their N-O levels.

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## INGREDIENTS

PRIME contains a proprietary blend of ingredients designed to maximize N-O production through natural physiological processes. The ingredients include:

- *Beet root powder*
- *Quercetin (95%)*
- *L-citrulline*
- *Cultured celery juice extract*
- *Pomegranate extract (40 % ellagic acid)*
- *Shisandra chinensis extract (9% schisandrins)*
- *Hawthorn berry extract*
- *Pine bark extract (50%)*
- *ProBiora3® Nitric Oxide Probiotic Blend with 600 million colony-forming units of S. oralis, S. uberis and S. rattus*

Qivana has optimized the dosage of each of these ingredients to ensure that each packet of PRIME Nitric Oxide Activator maximizes N-O production. Beet root powder and natural fruit and vegetable extracts contain high levels of nitrate. The body converts this nitrate into nitrite, which is made available for N-O production.

Hawthorn berry extract has been shown to have very high nitrite reductase activity. This is the process by which N-O is synthesized from nitrite molecules. Including hawthorn berry extract in the PRIME supplement enhances the efficiency of N-O production.

Scientific research has validated the use of ProBiora3® Nitric Oxide Probiotic Blend for use as a supplement that improves oral flora. The bacteria in this probiotic blend enhance the conversion of nitrate to nitrite, increasing N-O levels.

## DIRECTIONS FOR USE

Take once or twice daily, 12 hours apart. Pour a small amount of powder on your tongue and allow to dissolve before swallowing. Two packets per day are recommended for the first 30 - 60

days as a loading phase. After 30-60 days, take one packet per day as a maintenance phase. It is best to take the product on an empty stomach, either early in the morning or just before dinner or bedtime at night.

## SIDE EFFECTS

There are no serious known side effects of PRIME. Some individuals experience mild gas shortly after taking the product. This is a normal side effect and indicates that the product is working to improve Nitric Oxide synthesis.

Because PRIME contains B-vitamins, taking the product shortly before bedtime may cause sleeplessness. If this is the case, take the PRIME supplement earlier in the evening, being careful to space doses at least 12 hours apart.

## CONTRAINDICATIONS & HEALTH WARNINGS

Keep out of reach of children. Pregnant or lactating women, people with low blood pressure and individuals taking nitrates for chest pain should consult a doctor before using this product. Because PRIME changes circulatory system functioning, it may increase the rate of medication absorption. Individuals taking vitamins or prescription medications should consult a physician before taking PRIME to make sure it is safe to use with other pharmaceutical interventions.

## NITRIC OXIDE INSTANT INDICATOR

### What is the Instant Indicator?

The PRIME Instant Indicator provides a method to track current Nitric Oxide levels. This at-home test allows real-time tracking of Nitric Oxide production before and after using the PRIME Nitric Oxide Activator.

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## How does the Instant Indicator work?

The N-O Instant Indicator measures the total Nitric Oxide available in the body by assessing N-O levels in a saliva sample. The test pad changes color depending on the amount of available N-O in the sample. Comparing the test pad color to the provided N-O color chart gives an accurate assessment of Nitric Oxide levels.

## Why is measuring N-O levels important?

Other Nitric Oxide supplements do not provide a method for measuring current Nitric Oxide levels. The Instant Indicator gives a baseline measurement of N-O levels before taking the product. Tracking Nitric Oxide levels before PRIME supplement use, shortly after taking the product, and later in the day gives an accurate measurement of fluctuations in Nitric Oxide levels over time. After several days or weeks of use of PRIME Nitric Oxide Activator, users report higher sustained Nitric Oxide levels. This indicates that the product is improving natural Nitric Oxide synthesis in the body and increasing general Nitric Oxide availability.

## DIRECTIONS FOR USE

The most accurate way to use the N-O Instant Indicator is to measure Nitric Oxide levels before and after taking the PRIME supplement. Take an N-O reading first thing in the morning before eating breakfast or drinking fluids. To obtain an accurate reading, place a small amount of saliva on the test pad by spitting, using a cotton swab or using a clean finger. The Instant Indicator should never be placed directly in the mouth. Approximately 20 minutes after taking the PRIME supplement, perform another reading to measure the improvement in available Nitric Oxide. Taking a third reading just before lunch provides a measurement of sustained N-O levels, giving an indication of whether the PRIME Nitric Oxide Activator dosage is appropriate.

## HOW TO OBTAIN THE MOST ACCURATE N-O READINGS

A variety of factors may affect Instant Indicator measurements of Nitric Oxide levels. Do not eat or drink for at least 30 minutes before taking a N-O reading. Using antiseptic mouthwash or antibiotics may eliminate oral bacteria that are an essential part of the N-O synthesis pathway. Avoid using mouthwash before using the Instant Indicator and be aware that use of antibiotics may affect results.



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\*These statements have not been evaluated by the Food and Drug Administration.  
This product is not intended to diagnose, treat, cure, or prevent any disease.