# *Theramine*™ Product Information

## Indications

***Theramine*** is intended for use in the management of pain syndromes including acute pain, chronic pain, fibromyalgia, neuropathic pain, and inflammatory pain. ***Theramine*** is a medical food that must be used under the active or ongoing supervision of a physician. Medical foods are developed to address the different or altered physiologic requirements that may exist for individuals with distinctive nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions, and drug therapies.[1]

Pain is a complex process that is mediated by neurotransmitters which transmit signals originating from a pain-inducing stimulus to specific centers in the brain where it is perceived. Pain is exacerbated by the presence of inflammation which increases sensitivity to pain-inducing stimuli. Patients with pain syndromes benefit from increased availability of the specific neurotransmitters involved in modulating the pain process complemented by antioxidants and anti-inflammatory agents that reduce inflammation. ***Theramine*** is formulated to provide a balance of neurotransmitters with well-defined roles in the modulation of pain and a blend of antioxidants, anti-inflammatory agents, and immunomodulators to moderate the effects of inflammation on the pain response.

## Ingredients

***Theramine*** is a proprietary formulation of neurotransmitter precursors (L-arginine, L-glutamine, L-histidine, choline bitartrate, 5-hydroxytryptophan), neurotransmitters (gamma-aminobutyric acid [GABA]), and a neuromodulator (L-serine); polyphenolic antioxidants (grape seed extract, cinnamon bark, cocoa); anti-inflammatory and immunomodulatory peptides (whey protein hydrolysate); and adenosine antagonists (cocoa, metabromine). Each of these ingredients has been specifically selected based on scientific support for their roles in the physiological processes involved in reduction of pain. These roles are summarized in this monograph in the section, *Scientific Support for Use of **Theramine** in Management of Pain Syndromes*.

All of the ingredients included in ***Theramine*** are classified as generally recognized as safe (GRAS) by the United States Food and Drug Administration (FDA). To qualify for GRAS status, a substance that is added to a food, including a medical food, has to be supported by data demonstrating that it is safe when consumed in amounts from these foods as they are typically ingested or prescribed.

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[1] As defined in the guidelines issued by the Center for Food Safety and Nutrition, United States Food and Drug Administration (FDA).

## ***Targeted Cellular Technology™***

***Theramine*** has been formulated using *Targeted Cellular Technology*, an integrated molecular system that facilitates the uptake and utilization of neurotransmitter precursors by target cells within the nervous system. This 5-component system consists of (1) specific neurotransmitter precursors; (2) a stimulus for the neuronal uptake of these precursors by specific neurons; (3) an adenosine antagonist that blocks the inhibitory effect of adenosine on neuronal activity (adenosine brake); (4) a stimulus to trigger the release of the required neurotransmitters from targeted neurons; and (5) a mechanism to prevent attenuation of the precursor response, a well known phenomenon associated with precursor administration.

Use of *Targeted Cellular Technology* improves the metabolic efficiency of neurotransmitter synthesis, thereby reducing the amounts of amino acid precursors needed to correct neurotransmitter imbalances. Use of *Targeted Cellular Technology* also insures that the appropriate amounts of neurotransmitter precursors are delivered to the target neurons with the appropriate timing. As such, *Targeted Cellular Technology* synchronizes the fluctuating demand for neurotransmitters with the availability of the precursor supply, which is especially important for processes that are controlled by circadian rhythms such as utilization of arginine for the production of nitric oxide (1).

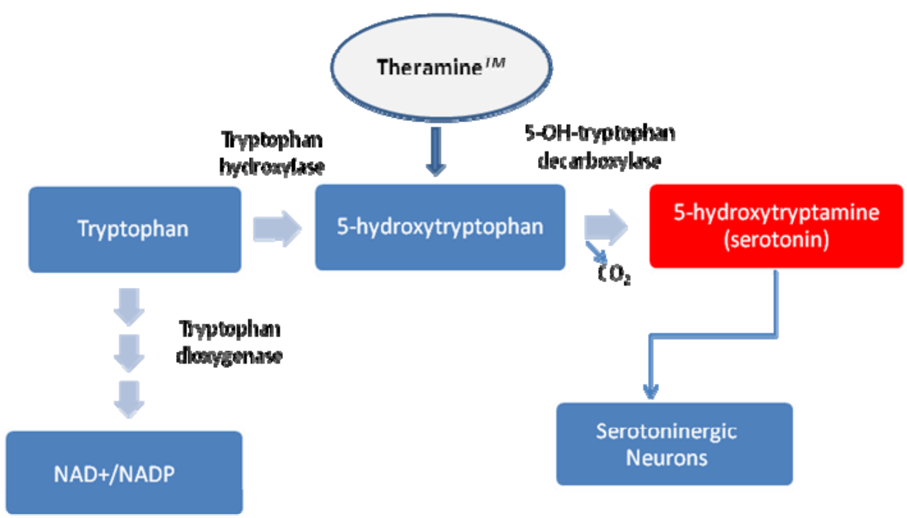
Previous attempts to provide an exogenous source of precursor amino acids in the quantities required to support neurotransmitter synthesis for individuals with specific needs necessitated that large amounts of these amino acids be added to the formulations. For patients whose requirements were considerably higher than normal, the amounts of exogenous amino acids that were needed were not practical to consume on a daily basis. In addition, ingestion of large amounts of amino acids increased the risk of adverse effects and the potential for attenuation of the response. Improving metabolic efficiency in uptake and utilization of neurotransmitter precursors by target neurons with *Targeted Cellular Technology* allows ingestion of smaller amounts of amino acids to elicit the same response, thus making daily dosing more feasible and reducing the potential for tolerance. Unlike pharmaceutical agents which are not innately involved in the pain process, and thus may lose their effectiveness in a relatively short period of time, the effectiveness of ***Theramine*** is not attenuated.

## **Metabolism**

***Theramine*** is a source of amino acids for patients with certain types of pain syndromes. These patients require additional amounts of tryptophan, arginine, glutamate, choline, and histidine to support synthesis of the neurotransmitters serotonin (5-hydroxytryptamine), nitric oxide, gamma-aminobutyric acid (GABA), histamine, and acetylcholine, respectively, which are active in the processes that mediate pain. Under normal physiological conditions, glutamate, arginine, and choline are metabolized as nonessential amino acids because endogenous synthesis is sufficient to satisfy metabolic demand. When needs are altered as in some types of pain syndromes, the usual rate of synthesis is no longer sufficient and these amino acids become conditionally essential, requiring that a supplemental amount be consumed. Histidine has also been considered nonessential for adults because it can be obtained from breakdown of skeletal muscle and hemoglobin; however, there is no evidence of histidine de novo synthesis in mammalian tissues and therefore an exogenous supply is important during times of increased needs to preserve muscle mass and plasma hemoglobin concentration.

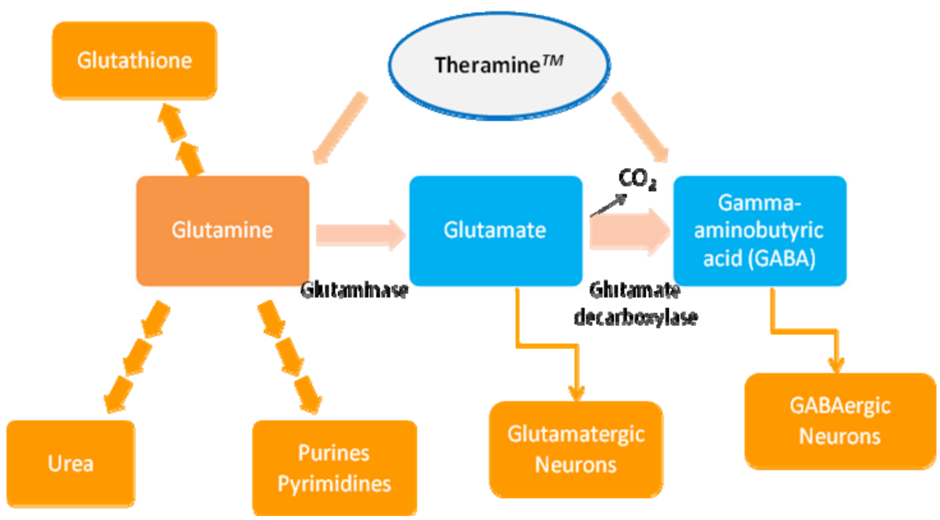
In contrast to the amino acids which are nonessential under normal conditions, tryptophan is an essential amino acid that must always be consumed from exogenous sources, as the enzymes required for its synthesis are absent in humans. Because it is an essential amino acid, the amount of tryptophan consumed determines the amount available to be divided among multiple pathways of utilization. Tryptophan is a precursor not only of serotonin, but also of the coenzymes nicotinamide adenine dinucleotide ($NAD^+$) and nicotinamide adenine dinucleotide phosphate (NADP) (Figure 1). The competition between these and other metabolic pathways for a limited supply of tryptophan restricts the amount of serotonin that can be produced from supplemental amounts of the amino acid. To overcome this limitation, ***Theramine*** provides 5-hydroxytryptophan, which is the immediate precursor of serotonin in the conversion pathway (Figure 1). The availability of this intermediate circumvents the limiting step in serotonin synthesis and lessens the dependence of serotonin levels on the amount of tryptophan consumed. By facilitating production of serotonin without requiring large amounts of tryptophan as a precursor, ***Theramine*** conserves the existing supply of the amino acid for other uses, thus improving metabolic efficiency.

**Figure 1. Competing Pathways of Tryptophan Metabolism**



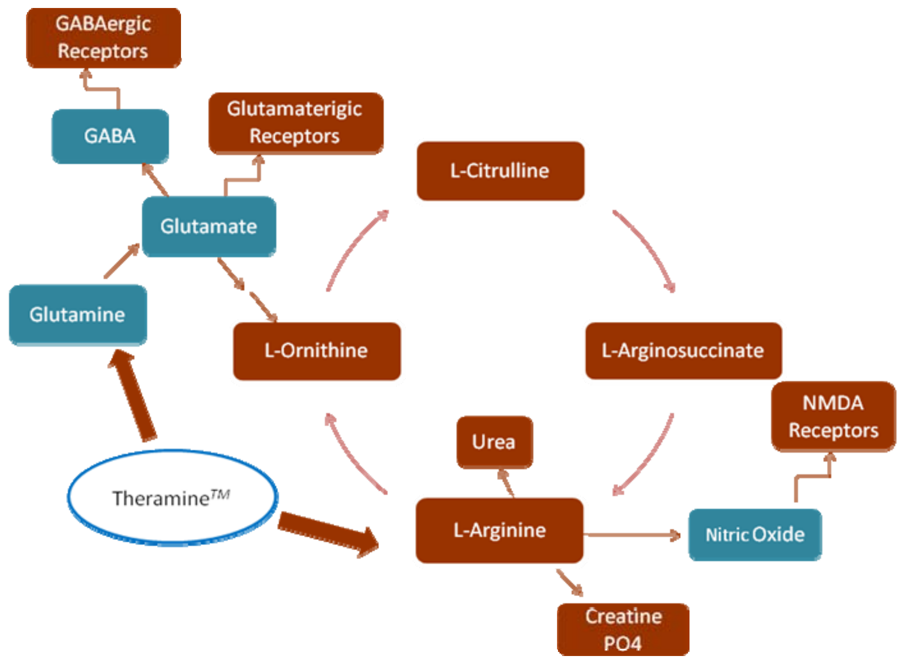
In contrast to tryptophan, glutamate is not normally dependent on exogenous sources and thus metabolic competition for glutamate will develop only under conditions of increased demand. For individuals with pain syndromes, the requirement for glutamate is higher than normal because additional amounts are needed to support GABA synthesis and to function as a neurotransmitter. Under normal physiological conditions, glutamate can be supplied by several sources including deamination of glutamine; however, glutamine is also utilized for synthesis of other compounds such as glutathione, purines, pyrimidines, and urea (Figure 2). These competitive demands for glutamine limit the amount of glutamate, and thus the amount of GABA available to function as neurotransmitters. ***Theramine*** improves metabolic efficiency by increasing the available supply of both glutamine and GABA. Additional glutamine insures that there is sufficient glutamate to function as a neurotransmitter and as a precursor for GABA synthesis without compromising other glutamine-dependent pathways. Additional GABA further insures that there is a sufficient amount of this neurotransmitter while conserving the available supplies of both glutamate and glutamine.

**Figure 2. Competing Pathways of Glutamine Metabolism**




The metabolic pathways which generate arginine are also normally sufficient to insure an adequate supply of this amino acid. Arginine is utilized as a precursor of nitric oxide, in addition to creatine phosphate and urea (Figure 3). When demand for nitric oxide is increased, arginine is diverted from synthesis of these other compounds. To compensate for the resulting decrease in arginine available to these pathways, glutamate is mobilized as a substrate for synthesis of additional amounts of arginine. ***Theramine*** improves metabolic efficiency by insuring that there is a sufficient amount of arginine available to satisfy the competitive demands which will otherwise deplete the glutamate body pool and upset neurotransmitter balance (nitric oxide, glutamate, and GABA), and that there is additional glutamine to conserve the existing supply of glutamate.

**Figure 3. Competing Pathways of Arginine Metabolism**




## Dosage

The recommended dose of ***Theramine*** is 1 or 2 capsules, taken 1 to 4 times daily as directed by a physician. As with any medical food, the best dosing protocol should be determined by assessment of individual needs. The amounts of each ingredient provided by ***Theramine*** at the doses recommended for pain reduction are provided in Table 1.

**Table 1. *Theramine* Composition**

| Ingredient | mg/kg body weight[1] |
|---|---|
| δ-aminobutyric acid (GABA) | 1.5 – 12.0 |
| choline bitartrate | 1.0 – 7.7 |
| L-arginine | 0.6 – 4.6 |
| Whey protein hydrolysate | 0.6 – 4.6 |
| L-histidine | 0.4 – 3.1 |
| L-glutamine | 0.4 – 3.1 |
| metabromine | 0.4 – 3.1 |
| 5-hydroxytryptophan (griffonia seed, 95% w/w) | 0.2– 1.9 |
| grape seed extract | 0.2 – 1.5 |
| L-serine | 0.2 – 1.5 |
| cinnamon bark | 0.2 – 1.5 |
| cocoa powder | 0.2 – 1.5 |

***Dosing range of 1 to 4 capsules***

***Theramine*** can be taken with pain medications such as once daily low dose aspirin (32 mg) or other nonsteroidal anti-inflammatory drugs (NSAIDs) such as low dose naproxen (250 mg) or tramadol (50 mg daily). If pain relief is obtained when ***Theramine*** is taken concurrently with other pain medications, then the drug dosage may be further tapered to lower levels under medical supervision. ***Theramine*** can also be used to manage the effective dose and dose-related side effects of pain medications. A randomized crossover study of patients with pain syndromes who were given ***Theramine*** concurrently with naproxen demonstrated that the effective dose of naproxen required to achieve pain reduction was decreased 75% from 4 times daily prior to use of ***Theramine*** to once daily after use. This study is described in greater detail in this monograph in the section, *Clinical Support for the Use of Theramine in Pain Syndromes.*

## Side Effects

As with any amino acid therapy, headache, upset stomach, or dry mouth may be experienced in some people after beginning treatment with ***Theramine***. These symptoms are mild and temporary and can be managed by drinking plenty of fluids and careful dose titration. Symptoms are relieved by initially lowering the dose and increasing to a therapeutic level as tolerated. The ingredients in ***Theramine*** are regularly consumed in amounts similar to those obtained from the normal food supply

## Abbreviations and Definition of Terms

The abbreviations and terms used frequently in this monograph are summarized in Table 2.

**Table 2. Abbreviations and Definitions of Terms**

| Term/Abbreviation | Definition |
|---|---|
| Anti-inflammatory | Inhibition of synthesis and release of chemicals that initiate and sustain an inflammatory response |
| Antinociception | Reduction of pain through inhibition of nociceptor activity |
| Antioxidant | Protects against oxidative cell damage from exposure to free radicals |
| Excitatory Neurotransmitters | Mediators of neural signals that accelerate the rate of transmission through depolarizing postsynaptic neuronal membranes resulting in increased responsive to a stimulus or reduced responsiveness to a stimulus through stimulation of inhibitory mechanisms |
| GABAergic | Neurons that secrete gamma-aminobutyric acid |
| Glutamatergic | Neurons that secrete glutamate |
| Inhibitory Neurotransmitters | Mediators of neural signals that slow the rate of transmission through hyperpolarization of postsynaptic membranes; inhibit responsiveness to a stimulus |
| Immunomodulators | Prevent excessive or inadequate immune responses |
| Neuromodulators | Moderate responsiveness of neurons to stimulants |
| Neuropeptide | Long chain of amino acids which influence neuronal activity and may act as neurotransmitters |
| Neurotransmitter | Secreted by presynaptic neurons in response to an action potential generated by a stimulus, binds to postsynaptic neurons which alters their membrane properties resulting in transmission of a signal down the neural pathways to a specific center in the brain which interprets the signals to initiate a response |
| NMDA | N-methyl-D-aspartate receptors which release glutamate thereby stimulating release of substance P |
| Nociceptors | Receptors at terminal ends of nerve fibers that initiate pain signaling in response to noxious stimuli |
| Prostaglandins | Compounds derived from arachidonic acid that modulate the inflammatory response |
| Serotoninergic | Neurons that secrete serotonin |
| *Targeted Cellular Technology™* | A patent pending process that facilitates endogenous production, uptake, and utilization of neurotransmitter precursors. |

## Mechanism of Action

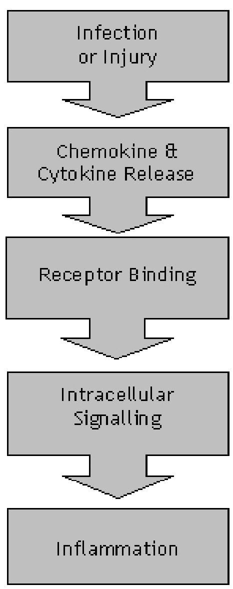
Understanding the mechanism of action of ***Theramine*** in the management of pain disorders requires a brief overview of the pain process. Pain is a complex series of reactions originating with an interaction between local pain receptors (nociceptors) and noxious stimuli and terminating in pain perception centers in the brain (2-4). The process of pain perception involves the coordinated responses of numerous ascending excitatory and descending inhibitory pathways (5). Pain reduction is accomplished by moderating responsiveness of the nociceptors to noxious stimuli, regulating the transmission of pain signals over the neural pathways of the peripheral and central nervous system, and controlling inflammation, which sensitizes the nociceptors to noxious stimuli. The neurotransmitters, neurotransmitter precursors, immunomodulators, antioxidants, and anti-inflammatory agents provided in ***Theramine*** have been chosen to function in a complementary manner to inhibit neuronal activity which exacerbates the transmission of pain signals and to mitigate the sensitizing effects of inflammation on neuronal responsiveness (2, 5-18).

Neurotransmitters function in the propagation of electrical impulses generated by nociceptor transduction of signals from noxious stimuli to specific areas in the brain where pain is perceived (19-21). These signals trigger afferent action potentials in the terminal endings of specialized nerve fibers which stimulate the release of neurotransmitters from presynaptic neurons into the synaptic cleft between adjacent neurons. The binding of these neurotransmitters to receptors on the postsynaptic neurons alters the electrical properties of the membranes which provokes a response from the neuron. The nature of this response depends on the chemical nature of the particular neurotransmitter involved. Depolarization of the membrane by excitatory neurotransmitters such as glutamate, acetylcholine, or serotonin will accelerate the rate of transmission of the electrical impulses, whereas hyperpolarization of the membrane by inhibitory neurotransmitters such as GABA will slow the rate of transmission (22-24). Deficiencies or imbalances between synthesis and secretion of excitatory and inhibitory neurotransmitters, or altered sensitivity of target neurons to neurotransmitter binding, will determine the intensity and duration of pain signals.

The responsiveness of neurons to pain signals is amplified by chemical or electrical phenomena that sensitize neurons to the incoming signals (20, 25-27). Sensitized neurons will discharge spontaneously with greater frequency over extended periods of time establishing the physiological basis for ongoing pain. Sensitized neurons also release increased amounts of neurotransmitters which augment the responsiveness of spinal cord neurons to all inputs leading to central sensitization (2, 20-21, 28-30). Activation of pain receptors not only amplifies cellular responsiveness to pain stimuli, but also attenuates neuronal sensitivity to antinociceptive receptor stimulants such as endogenous opioids (endorphins, dynorphins, and enkephalins), or exogenously administered opiates such as morphine (31-33).

The presence of inflammation also contributes to exacerbation of the pain response by increasing neuronal sensitivity to noxious stimuli (34). As part of the inflammatory response, cytokines, prostaglandins (specifically $PGE_2$), and other proinflammatory substances are released and accumulate at the site of tissue injury resulting in depolarization of the peripheral terminals of local nociceptors. In the spinal cord, an elevated concentration of proinflammatory $PGE_2$ increases the amounts of neurotransmitters released, depolarizes spinal cord neurons, and blocks the effects of inhibitory neurotransmitters. An increase in electrical activity in nociceptors sensitized by proinflammatory substances also stimulates the local release of chemicals which promote vasodilation, swelling, and the release of histamine from mast cells, thus sustaining inflammation-mediated neuronal sensitivity and prolonging pain.

**The Inflammatory Cascade**




Inflammation is a response to cellular injury due to infection or trauma which is mediated by serum proteins and cellular products released from phagocytic leukocytes, platelets, and lymphocytes that accumulate at the site of the injury. These compounds, which include cytokines (bradykinin) and lymphokines, (interleukins, and interferons), prostaglandins, leukotrienes, histamine, chemotaxins, platelet aggregating factors and neuropeptides, are responsible for a broad range of effects including changes in vascular permeability and modification of the electrochemical properties of cell membranes. Clinical manifestations of inflammation are redness, swelling, loss of function, and increased body temperature.

Intended to be protective as an acute response, prolonged inflammation contributes to the development of many disorders which include autoimmune diseases (multiple sclerosis, rheumatoid arthritis, type I diabetes, lupus erythematous) cardiovascular disorders (angioplasty re-stenosis, by-pass graft occlusion, transplant vasculopathy) and other disorders (fibromyalgia, asthma, inflammatory bowel disease, and transplant rejection).

Persistent pain is an outcome of hyperexcitability of the dorsal horn neurons in the spinal cord caused by severe or prolonged tissue or nerve injury (35). This hyperexcitable state potentiates the responsiveness of the dorsal horn neurons to noxious stimuli (hyperalgesia) and reduces the pain threshold (allodynia) (36). These effects are mediated by pre-synaptic N-methyl-D-aspartate (NMDA)-type glutamate receptors in the spinal cord which transmit pain signals from the periphery to the brain, and by the neuropeptide substance P which functions in a manner similar to a neurotransmitter except that it diffuses more widely and has longer lasting effects (37-41). Activation of NMDA receptors releases glutamate, an excitatory neurotransmitter which increases the neuronal discharge rate and stimulates the release of substance P (42-43). Since it is the interaction between glutamate and substance P that triggers the central nervous system response to noxious stimuli, treatments that target presynaptic NMDA receptors and substance P may be useful in ameliorating persistent pain (1, 9, 33, 36, 44-46).

Successful pain management is complicated by the presence of different types of pain, frequently occurring in various combinations in different pain syndromes. Based on the origin of the pain signal, 5 types of pain have been identified: visceral, somatic, referred, neuropathic, or psychogenic. Acute pain, which is nociceptive, is a result of visceral, somatic, and referred pain mechanisms (47-49). Chronic pain is a non-nociceptive phenomenon dominated by neuropathic and psychogenic mechanisms that contribute to the physical and mental suffering and disability characteristic of this pain syndrome (8). The transformation of acute pain to chronic pain involves changes in neuronal pathways (plasticity) that include sensitization to stimuli and increased signal transmission in the central nervous system (28, 50-51).

## Scientific Support for Use of *Theramine* in Management of Pain

The effectiveness of ***Theramine*** in management of pain syndromes is supported by an extensive body of experimental and clinical data which has identified specific roles for the ingredients in the formulation in the mechanism of pain reduction. These roles are summarized in Table 3.

**Table 3. Roles for *Theramine* Ingredients in the Pain Process**

| Ingredient | Effector Molecule | Function | Role |
|---|---|---|---|
| **GABA** | GABA | Inhibitory neurotransmitter | Dampens pain signals in the spinal cord and brain; activates glutaminergic nerve terminals which inhibit NMDA receptor activity and release of glutamate and substance P (52-54) |
| **Choline** | Acetylcholine | Inhibitory neurotransmitter | Promotes synthesis and potentiates the effects of nitric oxide and serotonin; reduces neuronal sensitivity and firing; inhibits NMDA receptor activity and production of substance P; suppresses proinflammatory cytokines by activation of the parasympathetic nervous system (55-58) |
| **Glutamine** | glutamine | Facilitator of neurotransmitter precursor uptake | Promotes synthesis of neurotransmitters (59-60) |
| | glutamate | Excitatory neurotransmitter | Inhibits NMDA receptors through activation of GABAergic receptors (61) |
| | GABA | Inhibitory neurotransmitter | Dampens pain signals in the spinal cord and brain; activates glutaminergic nerve terminals which inhibit NMDA receptor activity and release of glutamate and substance P (52, 62) |

| Ingredient | Effector Molecule | Function | Role |
|---|---|---|---|
| | Glutathione | Antioxidant; Immunomodulator | Regulates synthesis of leukotrienes (63-64) |
| **5-OH-tryptophan** | Serotonin | Excitatory neurotransmitter | Decreases and modulates pain signals from nerve cells in the spinal cord and brain; increases adenosine production by substance P neurons which inhibits release of substance P; inhibits NMDA receptors to further decrease levels of substance P (65-71) |
| **Serine** | Serine | Neuromodulator | Sensitizes opioid receptor systems to opioids, opioid-like agents, and other analgesics (natural opioids include endorphins, enkephalins, and dynorphins and synthetic opioids include morphine) (72-73) |
| **Arginine** | Nitric Oxide | Inhibitory and excitatory neurotransmitter; immunomodulator; anti-inflammatory | Inhibits transmission of afferent pain signals in the spinal cord; acts on some peripheral neurons; activates natural opioids; stimulates production of anti-inflammatory prostaglandins. inhibits NMDA receptor activity (4, 14, 74-77) |
| **Histidine** | Histamine | Excitatory neurotransmitter; Anti-inflammatory | Acts in the spinal cord and brain; stimulates production of glucocorticoids which inhibit prostaglandin-mediated inflammation and act synergistically with nitric oxide; inhibits NMDA receptors (77-80) |
| **Cocoa Powder** | caffeine | Adenosine antagonists | Bind to adenosine receptors to disinhibit the adenosine brake; adenosine has an inhibitory effect on neuronal activity (81-83) |
| **Grape seed extract** | Polyphenols | Antioxidant | Prevents attenuation of the response to neurotransmitter precursors; anti-inflammatory activity (84-86) |
| **Whey Protein Hydrolysate** | α-lactalbumin, β-Lactoglobulin, Glycomacropeptide, Lactoferrin | Opioid Agonist Immunomodulator Antioxidant Anti-inflammatory | α-lactalbumin and β-Lactoglobulin reduce pain through interactions with opioid receptors; other peptides reduce the effects of inflammation on pain (87-89) |
| **Metabromine** | caffeine, theobromine, procyanidins | Adenosine antagonists | Bind to adenosine receptors to disinhibit the adenosine brake; adenosine has an inhibitory effect on neuronal activity (90-93) |

## Nutrient Requirements of Pain Disorders

The nutrient requirements of most interest for patients with pain syndromes are the amino acids which function as neurotransmitters in the transmission of pain signals or which are utilized for synthesis of neurotransmitters involved in this process (15, 61, 94-102). The concept that nutrient requirements are modified in disease has long been recognized, and is supported by studies which have shown changes in plasma, urinary, and tissue levels of nutrients associated with changes in physiological endpoints reflective of the disease pathology (103). These requirements can be estimated by determining the level of intake at which a physiological response is normalized, indicating that the balance between intake and metabolic demand has been restored. For example, improvement in perceived intensity of back pain following consumption of increased amounts of 5-hydroxytryptophan, arginine, and glutamine from ***Theramine*** suggests that an additional allowance for tryptophan, arginine, and glutamate is needed by individuals with pain syndromes.

A large body of peer-reviewed published data supports the basis for increased requirements of arginine (104-107), tryptophan (108-112), choline (113-114), glutamine (113-114), serine (117-118), and histidine (119-120) in pain syndromes. Patients suffering from different types of pain syndromes show decreased blood levels of these amino acids despite having a sufficient intake of protein indicating that the needs for these amino acids are selectively increased in these patients. This observation may be explained by the competitive demands for these amino acids by different metabolic pathways which decrease the supply available to function in the pain process. Low blood levels of tryptophan accompanied by altered tryptophan metabolism have been frequently reported in patients with pain disorders (95). These patients also commonly exhibit reduced blood levels of 5-hydroxytryptophan, arginine, choline, GABA, histidine, and serine. Moreover, they also respond to oral administration of amino acid formulations by showing favorable changes in physiologic endpoints and improvements in clinical symptoms associated with pain, thus supporting a need for increased amounts of those amino acids which are reduced in the blood of patients with pain disorders.

A summary of the scientific support for the increased requirements of patients with pain disorders for the specific amino acids provided in ***Theramine*** is found in Table 4.

**Table 4. Basis for Assumption of Increased Nutrient Requirements in Pain Disorders**

| Nutrient | Biochemical and Physiologic Observations | Clinical Observations |
|---|---|---|
| **Choline** (119-122) | Reduced parasympathetic autonomic nervous system function | Decreased function of NMDA receptors; diminished responses to GABA and serotonin. |
| **Glutamine** (125-127) | Reduced blood levels; reduced blood and tissue glutathione | Increased muscle protein catabolism from metabolic stress |
| **GABA** (62, 128-129) | Reduced blood and brain levels | Loss of synaptic inhibition; seizures |
| **Tryptophan** (96-98, 130-135) | Reduced blood levels of tryptophan and serotonin | Depression, behavioral changes |

| Nutrient | Biochemical and Physiologic Observations | Clinical Observations |
|---|---|---|
| **Serine** (117-118,125, 134) | Reduced blood levels of glycine | Loss of sensitivity to both natural and synthetic inhibitors of pain |
| **Arginine** (1,105-106, 136-139) | Reduced plasma arginine and nitric oxide levels increase with dietary supplementation; rate-limiting for nitric oxide production; reduced production of anti-inflammatory prostaglandins | Increased plasma nitrates and exhaled nitric oxide with arginine supplements; circadian effects on utilization impacts timing of intake |
| **Histidine** (119-120, 134,140-141) | Reduced blood levels; decreased hemoglobin (source of histidine); increased cortisol | Increased cortisol requirements |
| **Polyphenolic Antioxidants (**7, 142-148**)** | Reduced nitric oxide; increased levels of proinflammatory prostaglandins | Altered platelet function; Decreased oxidative damage from administration of pro-oxidant compounds |

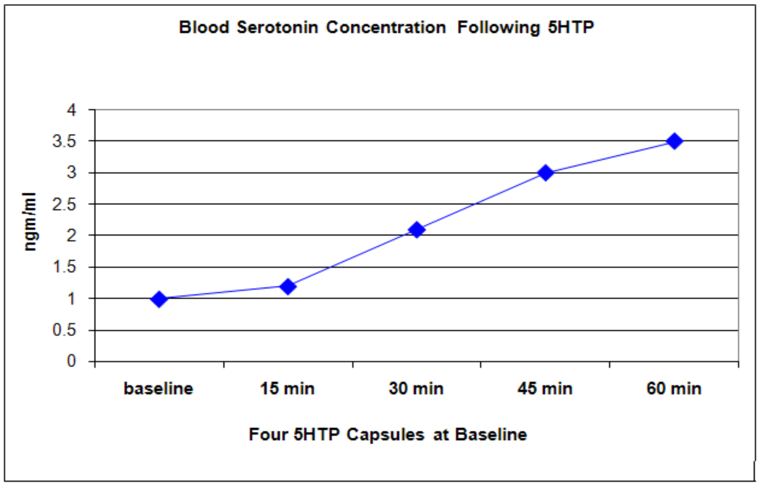
## Clinical Support for Use of *Theramine* in Management of Pain

The clinical benefits of a medical food can be validated by documented changes in biological, physiological, and clinical endpoints following administration of the formulation to individuals with a specific disease or disorder. For example, a medical food that provides specific amounts of amino acids is clinically validated by demonstrating an increase in blood levels of the selected amino acid or its metabolic end products (biological availability) or an improvement in an associated functional parameter (physiological/clinical response). Changes in blood levels of a neurotransmitter following ingestion of the amino acid precursor represents uptake and utilization of the amino acid by target cells, thus confirming biological availability of the increased amino acid when ingested from a medical food.

### Biological Availability

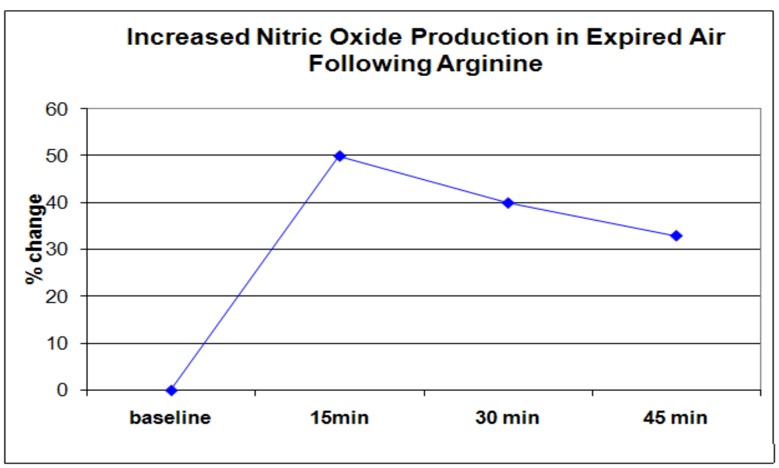
The biological availability of both 5-hydroxytryptophan and L-arginine has been demonstrated by observed changes in blood levels of the respective neurotransmitters following ingestion of these amino acids. Within 60 minutes after ingestion of 2000 mg of 5-hydroxytryptophan, a more than 3-fold increase in blood serotonin levels was observed confirming that 5-hydroxytryptophan is well-utilized by target tissues as a precursor of serotonin (Figure 1Figure 4).

**Figure 4. Effect of 5-hydroxytryptophan supplementation on blood serotonin levels**




**The biological availability of increased arginine for utilization as a precursor of nitric oxide has also been demonstrated by measurement of a 50% increase in nitric oxide concentration in expired air within 15 minutes of ingestion of a 15 mg dose in the *Targeted Cellular Technology* formulation**

**Figure 5. Effect of arginine supplementation on percent change in nitric oxide concentration in expired air**

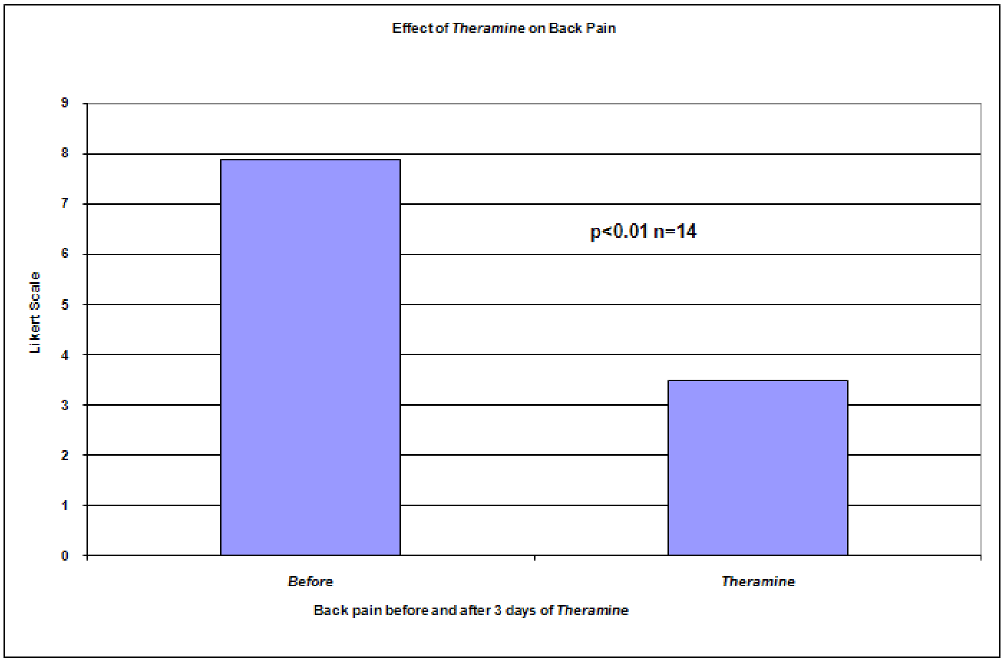



## Clinical Response

***Theramine*** has been clinically tested in crossover studies of patients with fibromyalgia, trigeminal neuralgia, back pain, headache, osteoarthritis, tendonitis, and post herpetic neuropathic pain based on physiologic and symptomatic pain assessment using visual analogue scales and Likert numeric scales as outcome measures.

The effect of ***Theramine*** on back pain was demonstrated in a controlled crossover study of 14 patients. After 3 days of treatment, pain symptoms were statistically significantly reduced by more than half of baseline values (p<0.01).

**Figure 6. Effects of *Theramine* Administration on Back Pain**




## Evidence Based Medicine and Medical Foods

The explicit methodologies used to determine "best evidence" were largely established by the McMaster University research group in 1978. The term "evidence based" was first used in 1990, and the term "evidence-based medicine" first appeared in the medical literature in 1992. There are now a large number of Evidenced Based Medical Systems that are designed for various purposes.

An evidence-based rating system is a science-based systematic evaluation of the strength of the evidence behind a statement. In the case of health claims, it would rate the strength of the evidence behind a proposed substance/disease relationship. A large number of evidence-based rating systems are currently in use today by physicians, dietitians and other health professionals. FDA has tentatively chosen to model its evidence-based rating system on that of the Institute for Clinical Systems Improvement (ICSI) as adapted by the American Dietetic Association with modifications specific to FDA. In making this tentative decision, FDA relied on criteria for evaluating evidence-based rating systems as reviewed and critiqued by the Agency for Healthcare Research and Quality (AHRQ).

The FDA has developed a system for evaluating the large body of information that is required to assess the value of therapeutic interventions. (Guidance for Industry, FDA Interim Evidence-Based Ranking System for Scientific Data July 10, 2003 http://www.cfsan.fda.gov/~dms/hclmgui4.html). The validation of therapeutic products has been accomplished using this method advanced by the FDA for assessment of the efficacy of therapies using the concept of Evidence Based Medicine. In the FDA model outlined below, the type, quantity, and consistency of evidence is evaluated and graded. The FDA model involves several elements:

“Each study would be characterized as a study design type. By categorizing the study, it automatically receives an initial study "rating" based on the type of experimental design, which is independent of the quality of the study. The rating of study design is based on the principle of minimizing bias. Only primary reports of data collection are rated. Reports that synthesize or reflect collections of primary reports are not considered part of the rating system although they may provide useful background information”.

1. Study Design Type One
   Randomized, controlled intervention trials

2. Study Design Type Two
   Prospective observational cohort studies

3. Study Design Type Three
   Nonrandomized intervention trials with concurrent or historical controls
   Case-control studies

4. Study Design Type Four
   Cross-sectional studies
   Analyses of secondary disease endpoints in intervention trials
   Case series

Furthermore, the FDA method provides additional criteria including Quantity and Consistency of Data:

1) **Quantity.** Considers the number of studies, the total number of individuals studied and the generalizability of the findings to the target population.

i. (***) means the number of studies and the number of individuals tested (from all studies of design types one and two that are of high quality (+) combined) are sufficiently large to comfortably generalize to the target population.

ii. (**) means there are a sufficient number of studies and individuals tested from study design type three and higher (i.e., study design types one and two) of at least moderate quality (Ø) but uncertainties remain as to generalizability to the target population.

iii. *) means that the number of studies and the number of individuals tested is insufficient to generalize to the target population.

2) **Consistency**. Considers whether studies with both similar and different designs report similar findings.

   i) (***) means a sufficient number of studies of design types one and two that are of high quality (+) have consistent results. Any inconsistencies should be explained satisfactorily.

   ii) (**) means there is a moderate consistency across all study levels.

(*) means that the results of studies are inconsistent.

Accordingly, the Medical Food ***Theramine*** has been validated using physiologic and symptomatic endpoints. These endpoints include documentation of the nutrient requirements, performance of physiologic endpoint trials using a controlled crossover design, and performance of controlled crossover design trials using pain scales with both visual analogue scales and Likert numeric scales.

There is a large body peer-reviewed published data supporting the nutritional requirements arginine, tryptophan, choline, glutamine, and histidine in pain syndromes as outlined above. The studies are consistent with little controversy concerning the nutrient requirements of these amino acids in pain syndromes.

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