

# Nattozimes®



## BACKGROUND INFORMATION

### PRODUCT DESCRIPTION

**Nattozimes®** is a proteolytic system from *Aspergillus oryzae* that is designed to be a substitute for nattokinase in dietary supplements used for cardiovascular or anti-inflammatory support. Nattokinase is a subtilisin-like protease produced by *Bacillus natto* and has properties that closely resemble plasmin and readily digests plasmin, fibrin, and similar synthetic substrates (Fujita et al, 1993)(Sumi et al, 1987). While nattokinase activity was originally discovered in fermentation extracts of *Bacillus natto*, *Bacillus subtilis* and *Aspergillus oryzae* also produce protease systems that exhibit nattokinase activity (Urano et al, 2002)(Chang et al, 2000). The nattokinase activity of a protease system is determined by a spectrophotometric assay that measures the system's ability to hydrolyze the peptide linkages of the standard fibrin substrate. Using this assay, NEC has established that **Nattozimes®** from *Aspergillus oryzae* is a 1:1 substitution for nattokinase.

### SUGGESTED USE

Suggested dosage is 1000 FU (1 capsule) taken 2 - 4 times a day, on an empty stomach.

### SUGGESTED STORAGE

Store **Nattozimes®** in a cool, dry location, away from light.

### FUNCTION

Natto is a vegetable cheese produced through the fermentation of boiled soybeans by the bacteria *Bacillus natto*. Popular for its taste and its perceived therapeutic actions, natto has been a staple of the Japanese diet for over a thousand years. As a folk remedy, natto has been traditionally used to treat cardiovascular disease. In the 1980's, Dr. Hiroyuki Sumi and his colleagues discovered that a protease enzyme is responsible for natto's positive cardiovascular effects (Sumi et al, 1987).

This enzyme, dubbed "nattokinase", has powerful antithrombic properties, which surpass those of even urokinase, giving it vast therapeutic potential. While this enzyme has been safely used in Japan for over 20 years, it was not on the list of enzymes recognized for use in dietary supplements prior to 1994; and therefore the enzyme was submitted to the FDA as a New Dietary Supplement Ingredient. Unfortunately on January 27, 2003 the FDA rejected the submission, and deemed a "protease from *Bacillus natto*" as misbranded under DSHEA. Recognizing the need for a "natto" type enzyme in the U.S. dietary supplement market, National Enzyme Company set out to develop a protease system that has the same *in vitro* activity as nattokinase, but is from a source organism that is already accepted for use in dietary supplements. **Nattozimes®** is the product of this search.

Nattokinase has been used in Japan to treat heart disease and inflammatory disease for over twenty years. The fibrinolytic and antithrombic activities of nattokinase explain these applications. **Nattozimes®** exhibits these same activities *in vitro*, demonstrating that **Nattozimes®** is an excellent substitute for nattokinase in supplements intended to provide cardiovascular or anti-inflammatory support. *In vitro*, animal studies, and human trials have demonstrated that nattokinase has powerful antithrombic activity (Sumi et al, 1987)(Sumi et al, 1990)(Fujita et al, 1993)(Fujita et al, 1995). *In vitro* studies clearly show that nattokinase not only actively degrades plasmin and fibrin, important components of thrombi, but that its actions are longer lasting than some standard antithrombic therapies (Sumi et al, 1987)(Fujita et al, 1993). These *in vitro* findings were further supported by animal models which showed that not only could nattokinase be absorbed through the intestinal tract, but that it acts to dissolve experimental blood clots *in vivo* (Sumi et al, 1990)(Fujita et al, 1995). Human trials performed by Daiwa Pharmaceutical Company confirmed that previous findings are also applicable to human subjects (<http://www.daiwa-pharm.com>). While the findings for nattokinase are impressive, it is not the only protease shown to be beneficial for the use in cardiovascular support. Proteases have been extensively studied, since the 1960's, for their fibrinolytic and antithrombic effects,

and many have shown great potential to improve blood fluidity and reduce platelet aggregation (Maurer, 2001)(Larsson et al, 1988)(Taussig and Batkin, 1988)(Felton, 1980). Of particular interest, proteases from *Aspergillus oryzae* have been shown to form complexes with alpha 2-macroglobulins. These complexes have powerful antithrombic effects, *in vivo* (Larsson et al, 1988).

Inflammation, regardless of its organic cause, results from a pro-inflammatory cascade involving the generation of proinflammatory cytokines. Extravascular fibrin deposition has been shown to activate pro-inflammatory cytokines, leading to localized inflammation and macrophage adhesion (Szaba and Smiley, 2002). This fibrin induced inflammation and macrophage adhesion is theorized by many to be responsible for the pathogenesis of a variety of chronic illnesses including heart disease, senile dementia, and fibromyalgia. Proteases have great potential for the treatment of chronic inflammatory conditions, because

they can interfere with two parts of the inflammatory cascade; thus breaking the self-sustaining inflammatory cycle. Since the 1960's proteases have been studied for their role in the treatment of inflammation and inflammatory disorders. In both animal and human trials, proteolytic enzymes have repeatedly been shown to significantly reduce inflammation resulting from sickness or injury (Ryan, 1967)(Smyth et al, 1967)(Shaw, 1969)(Kumakura et al, 1988)(Lomax, 1999). Early studies pointed entirely to the antithrombic and fibrinolytic aspects of proteases to explain this phenomenon. However, studies by Parmely and others indicate that, in addition to degrading fibrin, microbial proteases may actually inactivate pro-inflammatory cytokines to prevent or attenuate inflammatory cascades. Evidence suggests this may be accomplished through hydrolysis of tumor necrosis factor alpha (TNF $\alpha$ ) and/or interferon gamma (IFN $\gamma$ ). These actions of protease explain why both nattokinase and NEC's **Nattozimes**<sup>®</sup> are useful in dietary supplements designed to provide anti-inflammatory support.

## **SIDE EFFECTS, CONTRAINDICATIONS, AND DRUG INTERACTIONS**

Supplemental enzymes are considered safe and are well tolerated by most individuals. However, sensitivity to *Aspergillus* enzymes has been implicated in the pathogenesis of Crohn's Disease (Wiewrodt et al, 1995). For this reason, persons with Crohn's should not take **Nattozimes**<sup>®</sup>, unless otherwise indicated by their doctor. Rare reactions to supplemental enzymes may be seen in individuals who have extreme allergies to fungi or fungal spores. These reactions include rashes, nausea, vomiting, and possibly asthmatic reactions (Sen et al, 1998)(Doekes et al, 1999). Persons with extreme fungal allergies are cautioned against the use of **Nattozimes**<sup>®</sup>. Persons with known allergies to fungal products (i.e. penicillin, certain cheeses, etc.) are

cautioned when using **Nattozimes**<sup>®</sup> because there may be cross reactivity to these products that could trigger similar allergic responses. Consumption of proteolytic enzymes may increase clotting time. For this reason, **Nattozimes**<sup>®</sup> may interact with antithrombic medications leading to excessive bleeding. Persons suffering from clotting disorders or undergoing antithrombic therapy, including aspirin therapy and Warfarin, should consult their health care provider before using **Nattozimes**<sup>®</sup>. While there is no evidence that **Nattozimes**<sup>®</sup> could be dangerous to children or developing fetuses, women who are pregnant or nursing should contact a qualified health care practitioner before taking **Nattozimes**<sup>®</sup>.

*The information contained in this rationale is intended for educational purposes only. It is neither to be used to market or advertise a product nor to make labeling claims. The FDA and FTC have strict regulations concerning how information can be used in promoting a dietary supplement, and it is recommended that adherence to these regulations be followed.*