

BACKGROUND INFORMATION

PRODUCT DESCRIPTION

Serrazimes® is a proteolytic enzyme system derived from *Aspergillus oryzae* and *Aspergillus melleus* that is designed as an alternative for Serrapeptidase (a.k.a. serratio-peptidase and serrapeptase) in dietary supplements used for cardiovascular, anti-inflammatory, respiratory, or immune support. Serrapeptidase is a 50-kDa, alkaline metalloprotease that works to activate the Hageman factor-kallikrein-kinin systems of mammals and directly degrades or inhibits IgG and IgA immune factors as well as the regulatory proteins α -2-macroglobulin, α -2-antiplasmin, and antithrombin III (Molla et al, 1989)(Maeda and Molla, 1989). While originally isolated from *Serratia marcescens*, a bacteria found in the gut of the Japanese silk worm, Serrapeptidase activity is found in fermentation extracts of *Serratia E-15*, *Aspergillus oryzae*, and *Aspergillus melleus*. (Salamone and Wodzinski, 1997). The Serrapeptidase activity of a proteolytic system can be determined using a spectrophotometric assay that measures the system's ability to hydrolyze a standard casein substrate. Using this tool, NEC has established that **Serrazimes®** is a 1:1 enzymatic substitution for Serrapeptidase.

FUNCTION

Serrapeptidase is a protease initially isolated from *Serratia marcescens*, a potentially pathogenic bacteria, found in the gut of the Japanese silkworm. Recognized as a pharmaceutical agent and sold under the names Danzen and Aniflazyme, Serrapeptidase has wide clinical use in Asia and Europe for the treatment of assorted inflammatory disorders (Rothschild, 1991). In recent years, recognition of the efficacy of this product has led to growing interest in the US dietary supplement market. Despite international regulations, the product's efficacy and availability over the internet has fueled its popularity in the US dietary supplement industry where it is used for anti-inflammatory support, cardiovascular support, respiratory support, and as an adjunct to antibiotic therapy. Recognizing the potential for a "Serrapeptidase-type" enzyme in the U.S. dietary supplement market, National Enzyme Company set forth to develop a protease system that has the same *in vitro* activity as Serrapeptidase, but that is from a source organism(s) that has a long history of safe use in dietary supplements. **Serrazimes®** is the product of this search.

Serrapeptidase has been used in Europe and Asia to treat heart disease, inflammatory diseases, and bacterial infections for over 25 years. The proteolytic activities of Serrapeptidase explain these applications. **Serrazimes®** exhibits these same proteolytic activities *in vitro*, demonstrating that **Serrazimes®** is an excellent alternative for Serrapeptidase in supplements intended to provide cardiovascular, anti-inflammatory, respiratory, or immune support.

Since the 1960's plant and microbial proteases have been studied for their role in the treatment of inflammation and inflammatory disorders. In both animal and human trials, proteolytic enzymes, from a variety of sources, 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 research on the anti-inflammatory actions of proteases pointed entirely to their antithrombic and fibrinolytic aspects 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 α) and/or interferon gamma (IFN γ). Numerous human trials have shown Serrapeptidase to be highly effective for treating the inflammation resulting from carpal tunnel syndrome, surgery/injury, and breast engorgement (Mazzone et al, 1990)(Kee et al, 1989)(Esch et al, 1989)(Panagariya and Sharma, 1999)(Snowden et al, 2001)(Tachibana et al, 1984). **Serrazimes®** shows *in vitro* activity similar to Serrapeptidase, but uses a protease system from *Aspergillus melleus* and *Aspergillus oryzae*. Like Serrapeptidase, protease from *Aspergillus melleus* has been shown both *in vitro* and *in vivo* to significantly inhibit inflammatory responses (Fossati, 2000). However, in a head to head *in vivo* trial between protease from *Aspergillus melleus* and Serrapeptidase, protease from *Aspergillus melleus* not only showed better anti-inflammatory results than Serrapeptidase, but it also showed fewer side effects (Bracale and Sevetella, 1997). For these reasons, it is clear that **Serrazimes®** is not only an adequate substitution for Serrapeptidase in anti-inflammatory products, it may even be the better choice.

CARDIOVASCULAR SUPPORT

Proteases may play an important role in minimizing the effects of heart disease and in the prevention of heart attacks. In heart disease, blood flow to the heart is blocked, either by a blood clot or by aggregated arterial plaques (atherosclerosis). More and more, the medical community is coming to recognize that cardiovascular diseases like atherosclerosis and heart attack are actually symptoms of inflammatory venous disease. A clinical study of 40 patients suffering from inflammatory venous disease tested the efficacy of Serrapeptidase in the treatment of thrombophlebitis (Bracale and Selvetella, 1997). Serrapeptidase showed positive results in the treatment of this disorder for a majority of patients. However, this same study also tested the effectiveness of *Aspergillus melleus* protease for this condition. *Aspergillus* protease was shown to be superior to Serrapeptidase in both effectiveness and tolerability.

RESPIRATORY SUPPORT

Because of their anti-inflammatory and mucolytic properties, proteases have been studied for the treatment of chronic, non-viral, respiratory disorders including sinusitis, otitis, and asthma since the 1960's (Mazzone et al, 1990)(Majima et al., 1990) (Majima et al., 1988)(Ryan, 1967). Studies on Serrapeptidase and other proteases show that treatment with proteases can result in marked improvement in mucous viscosity and the inflammation of mucous membranes. In a head to head study, protease from *Aspergillus melleus* and Serrapeptidase both showed the ability to improve the viscoelasticity and clearance of sputum (Kase et al, 1982). However, caution should be used when administering Serrapeptidase to patients with symptoms of respiratory infections. While other proteases historically used as dietary supplements have actually been shown effective in treating viral infections, in vitro studies, animal studies, and adverse event reports indicate that Serrapeptidase may have the potential to increase both the incidence and severity of certain viral infections, including influenza and pneumonia (Maeda and Molla, 1989)(Hirahara et al, 1989) (Kleine et al, 1995). For this reason, persons with compromised immune systems, such as HIV infected patients, chemotherapy patients, or organ transplant patients, should be cautious in the use of Serrapeptidase. There is no evidence to suggest that **Serrazimes**[®] elicits the same adverse reactions.

ANTIBACTERIAL SUPPORT

Serrapeptidase has been shown to augment the activity of numerous antibiotic agents, including ampicillin, ciclacillin, cephalixin, minocycline, and cefotiam (Selan et al, 1993)(Aratami et al, 1980)(Ishihara et al, 1983). A study of the interaction between proteases from *Aspergillus melleus* and erythromycin shows that this protease has similar capabilities. In one such study pharmacologic synergism between this protease and erythromycin allowed the antibiotic to better penetrate and sterilize bronchial mucosa (Braga et al, 1992).

SIDE EFFECTS, CONTRAINDICATIONS, AND DRUG INTERACTIONS

Systemically used proteases are known to have antithrombic properties. Persons who suffer from clotting disorders or who are on antithrombic medications, such as warfarin, coumadin, or aspirin therapy may experience increased clotting times when using systemic proteases. Such persons should consult a physician prior to taking systemic doses of any protease, including **Serrazimes**[®]. Due to its effects on vascular permeability, the absorption and tissue distribution of antibiotics may be increased when administered concomitantly with **Serrazimes**[®] (Braga et al, 1992). Persons on antibiotics should consult their physicians prior to taking **Serrazimes**[®]. This product may irritate gastric ulcers.

REFERENCES:

- Aratani, H et al. "Studies On The Distributions Of Antibiotics In The Oral Tissues: Experimental Staphylococcal Infection In Rats, and Effect Of Serratiopeptidase On The Distributions Of Antibiotics." *Jpn J Antibiot.* 1980. 33(5): 623.
- Braga, PC et al. "Effects Of Seaprose On The Rheology of Bronchial Mucus In Patients With chronic Bronchitis. A Double-blind study vs Placebo." *Int J Clin Pharmacol Res.* 1993. 13(3): 179-85.
- Braga, PC et al. "The Influence of Seaprose on Erythromycin Penetration Into Bronchial Mucus In Bronchopulmonary Infections." *Drugs Exp Clin Res.* 1992. 18(3): 105-11.
- Bracale, G. and Selvetella, L. "Clinical Study Of The Efficacy Of And Tolerance To Seaprose S In Inflammatory Venous Disease. Controlled Study Versus Serratio-peptidase." *Minerva Cardioangiol.* 1996. 44(10): 515.
- Esch, PM. et al. "Reduction Of Postoperative Swelling. Objective Measurement Of Swelling Of The Upper Ankle Joint In Treatment With Serrapeptase—A Prospective Study." *Fortschr Med.* 1989. 107(4): 67.
- Fossati, A. "Antiinflammatory effects of seaprose-S on various inflammation models." *Drugs Exp Clin Res.* 2000. 24(6): 263-70.
- Hirahara, K. et al. "A Case Of Pneumonitis due to Serrapeptase." *Nihon Kyobu Shikkan Gakkai Zasshi.* 1989. 27(10): 1231.
- Ishihara, Y. et al. "Experimental Studies On Distribution of Cefotiam, A New Beta-lactam Antibiotic , In The Lung And Trachea Of Rabbits. II. Combined Effect With Serrapeptidase." *Jpn J Antibiot.* 1983. 36(10): 2665.
- Kase, Y et al. "A new Method For Evaluating Mucolytic Expectorant Activity And Its Application. II. Application To Two Proteolytic Enzymes, Serratiopeptidase and Seaprose." *Arneimittelforschung.* 1982. 32(4): 374-8.
- Kee, WH. et al. "The Treatment Of Breast Engorgement With Serrapeptase (Danzen): A Randomised Double-blind Controlled Trial." *Singapore Med J.* 1989. 30(1): 48.
- Kleine, MW et al. "The Intestinal Absorption of Orally Administered Hydrolytic Enzymes and Their Effects in the Treatment of Acute Herpes Zoster as compared with those of oral Acyclovir Therapy." *Phytomedicine*, 1995.2(1): 7-15.
- Maeda, H. and Molla, A. "Pathogenic Potentials Of Bacterial Proteases." *Clin Chim Acta.* 1989. 185(3): 357.
- Majima, Y et al. "The Effect Of An Orally Administered Proteolytic Enzyme On The Elasticity And Viscosity Of Nasal Mucus." *Arch Otorhinolaryngol.* 1988. 244(6): 355.
- Majima, Y et al. "Effects Of Orally Administered Drugs On Dynamic Viscoelasticity Of Human Nasal Mucus." *Am Rev Respir Dis.* 1990. 141(1): 79.
- Mazzone, A. et al. "Evaluation Of Serratio Peptidase In Acute Or Chronic Inflammation Of Otorhinolaryngology Pathology: A Multicentre, Double-blind, Randomized Trial Versus Placebo." *J. Int Med Res.* 18(5): 379.
- Molla, A. et al. "Activation of Hageman Factor And Prekallikrein And Generation Of Kinin By Various Microbial Proteinases." *J Biol Chem.* 1989. 264(18): 10589.
- Moretti, M. et al. " Effects of Seaprose On Sputum Biochemical components in Chronic Bronchitic Patients: A Double-Blind Study VS. Placebo." *Int J Clin Pharmacol Res.* 1993. 13(5): 275-80.

REFERENCES CONTINUED:

- Ovartlarnporn, B. et al. "Medication-induced Esophageal Injury: Report Of 17 Cases with Endoscopic Documentation." *Am J Gastroenterol.* 1991. 86(6): 748.
- Panagariya, A. and Sharma, AK "A Preliminary Trial Of Serratiopeptidase In Patients With Carpal Tunnel Syndrome." *J Assoc Physicians India.* 1999. 47(12): 1170.
- Parmely, MJ., et al. "Proteolytic Inactivation of Cytokines by *Pseudomonas aeruginosa*." *Infect and Immune.* 1990. 58:3009.
- Rothschild, J. "Clinical Use of Serrapeptase: An Alternative To Non-Steroidal Anti-inflammatory Agents." *The American Chiropractor.* 1991. p. 17.
- Ryan, RE. "A Double-Blind Clinical Evaluation Of Bromelains In The Treatment Of Sinusitis." *Headache.* April 1967:7(1):13-7.
- Salamone, PR. and Wodzinski RJ. "Production, Purification, and Characterization Of A 50-kDa Extracellular Metalloprotease Form *Serratia marcescens*." *Appl Microbiol Biotechnol.* 1997. 48(3): 317.
- Selan, L. et al. "Proteolytic Enzymes: A New Treatment Strategy For Prosthetic Infections." *Antimicrob Agents Chemother.* 1993. 37(12): 2618.
- Snowden, HM. et al. "Treatments For Breast Engorgement During Lactation." *Cochrane Database Syst Rev.* 2001. (2): CD000046.
- Tachibana, M. et al. "A Multi-centre, Double-blind Study Of Serrapeptase Versus Placebo In Post-antrotomy Buccal Swelling." *Pharmatherapeutica.* 1984. 3(8): 526.