



As listed in the Physicians' Desk Reference (PDR)

IMMUNOCAL®

PDR® 2005

2003

NUTRACEUTICAL

(Bonded cysteine supplement)

Powder Sachets

DESCRIPTION and CLINICAL PHARMACOLOGY

IMMUNOCAL® is a U.S. patented natural food protein concentrate in the FDA category of GRAS (generally recognized as safe) which assists the body in maintaining optimal concentrations of glutathione (GSH) by supplying the precursors required for intracellular glutathione synthesis. It is clinically proven to raise glutathione values (Lands et al, 1999).

Glutathione is a tripeptide made intracellularly from its constituent amino acids L-glutamate, L-cysteine and glycine. The sulfhydryl (thiol) group (SH) of cysteine serves as a proton donor and is responsible for the

biological activity of glutathione. Provision of this amino acid is the rate-limiting factor in glutathione synthesis by the cells since cysteine is relatively rare in foodstuffs and furthermore, if released as the free amino acid, is toxic and spontaneously catabolized in the gastrointestinal tract and blood plasma.

ImmunoCAL® is a bovine whey protein isolate specially prepared so as to provide a rich source of bioavailable cysteine. Following digestion, the cysteine remains as the stable form cystine (2 molecules of cysteine linked by disulfide bond) and glutamylcystine. After absorption, these dipeptides travel safely in the blood stream and readily enter the cells to release free cysteine for intracellular glutathione synthesis. ImmunoCAL® can thus be viewed as a cysteine delivery system.

The disulphide bond in cystine is pepsin and trypsin resistant but may be split by heat, low pH or mechanical stress releasing free cysteine. When subject to heat or shearing forces (inherent in most extraction processes), the fragile disulfide bonds within the peptides are broken and the bioavailability of cysteine is greatly diminished.

Glutathione is a tightly regulated intracellular constituent and is limited in its production by negative feedback inhibition of its own synthesis through the enzyme gamma-glutamylcysteine synthetase, thus greatly minimizing any possibility of overdose.

Glutathione has multiple functions:

1. It is the major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds, as well as maintaining exogenous antioxidants such as vitamins C and E in their reduced (active) forms.
2. Through direct conjugation, it detoxifies many xenobiotics (foreign compounds) and carcinogens, both organic and inorganic.
3. It is essential for the immune system to exert its full potential, e.g. (1) modulating antigen presentation to lymphocytes, thereby influencing cytokine production and type of response (cellular or humoral) that develops, (2) enhancing proliferation of lymphocytes thereby increasing magnitude of response, (3) enhancing killing activity of cytotoxic T cells and NK cells, and (4) regulating apoptosis, thereby maintaining control of the immune response.
4. It plays a fundamental role in numerous metabolic and biochemical reactions such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport and enzyme activation. Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system and the lungs.

INDICATIONS AND USAGE

IMMUNOCAL® is a natural food supplement and as such is limited from stating medical claims per se. Statements have not been evaluated by the FDA. As such, this product is thus not intended to diagnose, cure, prevent or treat any disease.

Glutathione augmentation is a strategy developed to address states of glutathione deficiency, high oxidative stress, immune deficiency, and xenobiotic overload in which glutathione plays a part in the detoxification of the xenobiotic in question. Glutathione deficiency states include, but are not limited to: HIV/AIDS, chemical and infectious hepatitis, prostate and other cancers, cataracts, Alzheimer's, Parkinsons, chronic obstructive pulmonary disease, asthma, radiation poisoning, malnutritive states, arduous physical stress, aging, and has been associated with sub-optimal immune response. Many clinical pathologies are associated with oxidative stress and are elaborated upon in numerous medical references.

Low glutathione is also strongly implicated in wasting and negative nitrogen balance (Droge and Holm, 1997), notably as seen in cancer, AIDS, sepsis, trauma, burns and even athletic overtraining. Glutathione supplementation can oppose this process and in AIDS, for example, result in improved survival rates (Herzenberg et al, 1997).

CONTRAINDICATIONS

IMMUNOCAL® is contraindicated in individuals who develop or have known hypersensitivity to specific milk proteins.

PRECAUTIONS

Each sachet of IMMUNOCAL® contains nine grams of protein. Patients on a protein-restricted diet need to take this into account when calculating their daily protein load. Although a bovine milk derivative, IMMUNOCAL® contains less than 1% lactose and therefore is generally well tolerated by lactose-intolerant individuals.

WARNINGS

Patients undergoing immunosuppressive therapy should discuss the use of this product with their health professional.

ADVERSE REACTIONS

Gastrointestinal bloating and cramps if not sufficiently rehydrated. Transient urticarial-like rash in rare individuals undergoing severe detoxification reaction. Rash abates when product intake stopped or reduced.

OVERDOSAGE

Overdosing on IMMUNOCAL[®] has not been reported

DOSAGE AND ADMINISTRATION

For mild to moderate health challenges, 20 grams per day is recommended, higher doses are recommended. Clinical trials in patients with AIDS, COPD, cancer and chronic fatigue syndrome have used 30-40 grams per day without ill effect. IMMUNOCAL[®] is best administered on an empty stomach or with a light meal. Concomitant intake of another high protein load may adversely affect absorption.

RECONSTITUTION

IMMUNOCAL[®] is a dehydrated powdered protein isolate. It must be appropriately rehydrated before use. Remains bioactive up to 12 hours after mixing. DO NOT heat or use a hot liquid to rehydrate the product. DO NOT use a high-speed blender for reconstitution. These methods will decrease the activity of the product.

Proper mixing is imperative. Consult instructions included in packaging.

HOW SUPPLIED

10 grams of bovine milk protein isolate powder per sachet.

30 sachets per box.

STORAGE

Store in a cool dry environment. Refrigeration is not necessary.

Patent no.'s: 5,230,902 - 5,290,571 - 5,456,924 - 5,451,412 - 5,888,552

REFERENCES

1. Baruchel S, Viau G, Olivier R. et al. Nutraceutical modulation of glutathione with a humanized native milk serum protein isolate, Immunocal[®]: application in AIDS and cancer. *In*: Oxidative Stress in Cancer, AIDS and Neurodegenerative Diseases. Ed.; Montagnier L, Olivier R, Pasquier C. Marcel Dekker Inc. New York, 447-461, 1998
2. Bounous G, Kongshavn P. Influence of protein type in nutritionally adequate diets on the development of immunity. *In*. Absorption and Utilization of Amino Acids Vol.II. Ed. M. Friedman. CRC Press, Inc., Fla. 2:219-32, 1989
3. Bounous G, Gold P. The biological activity of undenatured whey proteins: role of glutathione. *Clin Invest Med* 14:296-309, 1991
4. Bounous G, Baruchel S, Falutz J. Gold P. Whey proteins as a food supplement in HIV-seropositive individuals. *Clin Invest Med*. 16:3; 204-209, 1992
5. Bounous G. Whey protein concentrate (WPC) and glutathione modulation in cancer treatment. *Anticancer Res*. 20:4785-4792,2000
6. Bounous G. Immunoenhancing properties of undenatured milk serum protein isolate in HIV patients. *Int. Dairy Fed: Whey*: 293-305, 1998
7. Droge W, Holm E. Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction. *FASEB J*: 11(13):1077-1089, 1997
8. Herzenberg LA, De Rosa SC, Dubs JG et al. Glutathione deficiency is associated with impaired survival in HIV disease. *Proc Natl Acad Sci* 94:1967-72,1997
9. Kennedy R, Konok G, Bounous G et al.. The use of a whey protein concentrate in the treatment of patients with metastatic carcinoma: A phase I-II clinical study. *Anticancer Res*. 15:2643-50,1995
10. Lands LC, Grey VL, Smountas AA. Effect of supplementation with a cysteine donor on muscular performance. *J. Appl. Physiol*. 87:1381-1385, 1999
11. Locigno R, Castronovo V. Reduced glutathione system: Role in cancer development, prevention and treatment. *International Journal of Oncology* 19:221-236, 2001
12. Lomaestro B, Malone M. Glutathione in health and disease: pharmacotherapeutic issues. *Ann Pharmacother* 29: 1263-73,1995
13. Lothian B, Grey V, Kimoff RJ, Lands. Treatment of obstructive airway disease with a cysteine donor protein supplement: a case report. *Chest* 117:914-916, 2000
14. Meister A. Glutathione. *Ann Rev Biochem* 52:711-60,1983
15. Peterson JD, Herzenberg LA, Vasquez KK, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. *Proc.Natl. Acad. Sci*. 95:3071-3076, 1998
16. Watanabe A, Higachi K, Yasumura S. et al. Nutritional modulation of glutathione level and cellular immunity in chronic hepatitis B and C. *Hepatology*. 24:597A, 1996

Manufactured by Immunotec Research Ltd.