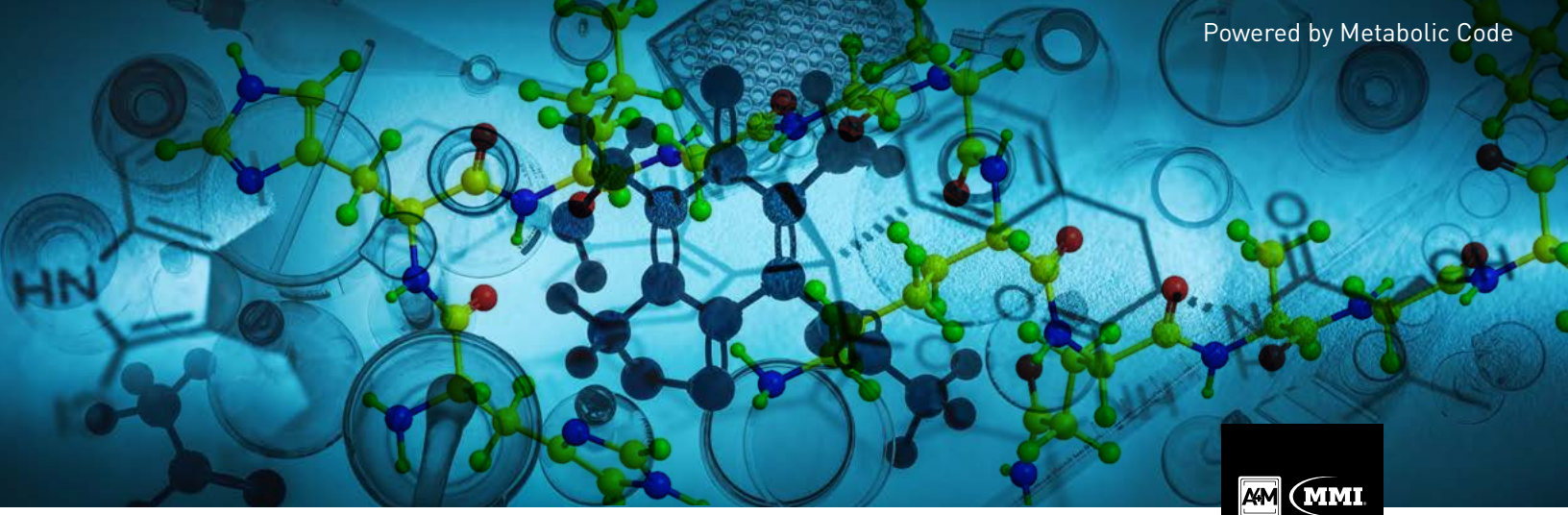


Peptide Therapy Handbook
For Healthcare Professionals

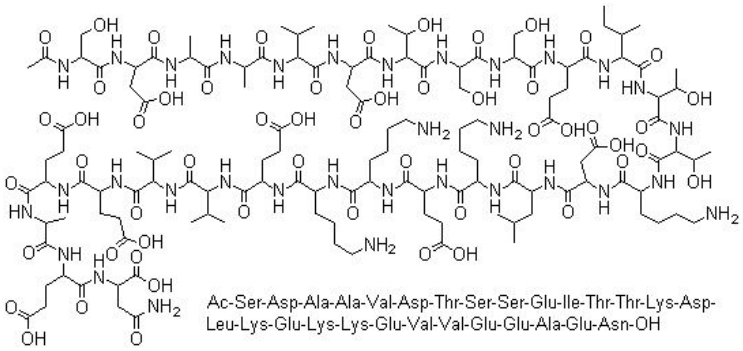
Thymosin alpha-1

Name(s):

- Thymosin alpha-1
- Thymalfasin
- Zadaxin™

Sequence:

Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys- Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH



Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH

Molecular Composition:

MW 3108.28 g/mol

Molecular Formula $C_{129}H_{215}N_{33}O_{55}$

Indications/Uses

Used for clinical conditions where immune support is necessary, including:

- Hepatitis B & C
- HIV/AIDS
- Cancer – non-small cell lung (NSCLC), hepatocellular, malignant melanoma
- Chemotherapy adjunct
- Chronic inflammatory conditions; autoimmunity
- Cystic fibrosis
- Lyme disease
- Blocks steroid-induced apoptosis of thymocytes
- Depressed response to vaccinations; adjunct to flu vaccine o Geriatric immune support
- DiGeorge's syndrome
- Other conditions requiring immune response modulation

Dosage:

SubQ General Dosage:

- 3mg/ml 5ml vial
- 1.5 mg SubQ every 3$^{r\ d}$ day
- Treatment from 2 weeks for viral infection and 3 months or longer for HIV/ cancer / Hepatitis B, C or complicated immune suppression or over-activation
- Multiple over-lap of usage

Zadaxin™ Dosage:

- 1.6 mg, injected SubQ, 2 times weekly for 6-12 months
- Patients weighing < 40 kg, dosage adjusted to 40 mcg/kg, 2 times weekly.
- May be used together with conventional antiretroviral regimens
- Individual dosage requirements may vary based on clinical presentation

Warnings and Cautions

- Thymosin alpha 1 peptide is reported safe in recommended dosages.
- Since 1979, thymosin alpha-1 is well tolerated. Tα1 has demonstrated a very favorable toxicity profile in more than 3,000 individuals treated to date, including patients with hepatocellular carcinoma, non–small-cell lung cancer, melanoma, and hepatitis B and C. [...]
- Thymosin alpha 1 has been reported to be well tolerated even in patients with decompensated liver disease, renal disease requiring hemodialysis and primary immunodeficient individuals.
- As with all injections, redness and pain at the site of injection may be present.
- Rare adverse reactions include erythema, transient muscle atrophy, polyarthralgia combined with hand edema, and rash.
- A transient increase in ALT to more than twice baseline value can occur during thymosin alpha 1 therapy. When ALT flare occurs, thymosin alpha 1 should generally be continued unless signs and symptoms of liver failure are observed.
- Use caution if administering to pregnant or nursing women.
- Do not use in individuals being deliberately immunosuppressed.
- Safety in pediatrics has not been established.

Summary

- Thymosin alpha-1 is a synthetic thymic peptide used to improve immune responses in times of need.
- Studies report thymosin alpha-1 : [...]
- Modulates innate immunity (pleiotropic)
- Improves Th1 immune responses and helps balance Th1/Th2 o Promotes T cell (Tregs) differentiation and maturation
- Decreases T-cell apoptosis

- Improves CD3+, CD4+ and CD8+
- Improves production of IL-1 beta, IFN-γ, IL-2, IL-3, IL-6, IL-10 o Improves NK cell activity and TNF-alpha
- Improves macrophages and B cells
- Up regulates MHC Class I expression in antigen expressing cell
- Tumor specific antigens; anti-tumor properties
- Inhibits viral replication
- Activates indoleamine 2,3-dioxygenase enzyme - dampens immunity
- Improves dendritic cell tryptophan catabolism
- Antioxidant properties – improves intracellular glutathione

Thymosin alpha 1 has been used to support immunity in over 3,000 patients and in over 70 clinical studies, either as monotherapy or in conjunction with current allopathic medicines., The lack of significant side effects with thymosin alpha 1 is in sharp contrast to other major immune response modulators such as IFN and IL-2, which can lead to flu-like symptoms including malaise, fever, headache, chills and pulmonary edema (with IL-2).

Thymosin alpha 1 helps the body induce effective host-derived immune effectors and balance the Th1 / Th2 arms of immunity. These effector cells improve various immunomodulatory properties that lead to augmentation of T lymphocyte function, including modulation of interleukin-2 (IL-2), stimulation of interferon-g (IFN-g) production, induction of T lymphocyte and natural killer (NK) cells and stimulation of thymopoiesis. Ta1 has also been reported to up-regulate MHC Class I expression in antigen-presenting cells. Additionally, Ta1 down-regulates the activity of terminal deoxynucleotide transferase (TdT) in TdT1 thymocytes, suggesting a role for Ta1 in thymocyte maturation. Ta1 has also been found to antagonize both activation induced (anti-CD3) and glucocorticoid-induced thymocyte apoptosis. It has also been reported that Ta1 stimulates activity of Indoleamine-2,3-Dioxygenase (IDO), leading to an increase in FoxP3 IL-10 producing regulatory T cells. This increase leads to feedback inhibition of cytokine production, hence dampening immune response to prevent a pro-inflammatory cytokine storm and possibly autoimmune phenomena.

Immune senescence, considered an aging process, has been related to a gradual decline in thymus function and thymic hormone production. The lack of thymic hormones may contribute to the decline in immune function, particularly the T cell component. In the elderly, antibody response after vaccination is compromised when compared to response in young. A similar diminished antibody response has been reported in patients with end-stage renal disease (ESRD) and in hemodialysis patients. In hemodialysis patients, this has been attributed to incompetence in T cell-mediated immune responses.

Since thymosin alpha-1 can enhance T-cell-dependent specific antibody production, Ta1 can help augment specific vaccine responses both in the elderly or in younger subjects in situations in which there are suboptimal quantities of immunizing antigen available.

Zadaxin™

Zadaxin (thymalfasin, SciClone Pharmaceuticals, China) is a thymosin alpha-1 peptide that has been evaluated for its immunomodulatory activities and related therapeutic potential in several diseases, including chronic hepatitis B and C, acquired immunodeficiency syndrome (AIDS), primary immunodeficiency diseases, depressed response to vaccination, and cancer. Zadaxin is currently in Phase III trials for the treatment of hepatitis C and in Phase II trials for hepatitis B in the US.

[1] GF Stefanini, FG Foschi, E Castelli , etal: Alpha-1-thymosin and transcatheter arterial chemoembolization in hepatocellular carcinoma patients: A preliminary experience Hepatogastroenterology 45: 209– 215,1998
[2] F Salvati, G Rasi, L Portalone , etal: Combined treatment with thymosin-alpha1 and low-dose interferon-alpha after ifosfamide in non-small cell lung cancer: A phase-II controlled trial Anticancer Res 16: 1001– 1004,1996
[3] G Rasi, E Terzoli, F Izzo , etal: Combined treatment with thymosin-alpha1 and low dose interferon-alpha after dacarbazine in advanced melanoma Melanoma Res 10: 189– 192,2000
[4] Zadaxin prescribing information SciClone Pharmaceuticals. www.scicloneinternational.com
[5] Goldstein AL. History of the discovery of the thymosins Ann N Y Acad Sci. 2007;1112: 1– 13.
[6] Garaco E, Pica F, Serafino A, et al. Thymosin alpha-1 and cancer: action on immune effector and tumor target cells. Ann NY Acad Sci. 2012;1269:26-33.
[7] Romani L, MorettiS, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. Ann NY Acad Sci. 2012;1269:1-6.
[8] Romani L, Bistoni F, Perruccio K, et al. Thymosin alpha 1 activates dendritic cell tryptophan catabolism and estraclishes a regulatory environment for balance of inflammation and tolerance. Blood. 2006;108(7):2265-74.
[9] Naylor PH. Zadaxin (thymosin alpha 1) for the treatment of viral hepatitis. Expert Opin Investig Drugs. 1999;8(3):281-7.
[10] Billich A. Thymosin alpha 21. SciClone Pharmaceuticals. Curr Opin Investig Drugs. 2002;3(5):698-707.
[11] HE C, Peng W, Li C, et al. Thymalfasin, a promising adjuvant therapy in small hepatocellular carcinoma after liver resection. Medicine (Baltimore). 2017;96(16):e6606.
[12] Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.
[13] Matteucci C, Grelli S, Balestrieri E, et al. Thymosin alpha 1 and HIV-1: recent advances and future prospectives. Future Microbiol. 2017;12:141-155.
[14] Lopez-Alcorocho J, Vartolome J, Cotonat T, Carreno V. Efficacy of prolonged interferonalpha treatment in chronic hepatitis B patients with HBeAb: comparison between 6 and 12 months of therapy. J Vir Hep. 1997;4(suppl 1):27-32.
[15] Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.
[16] Giuliani C, Napolitano G, Mastino A et al. Thymosin-alpha1 regulates MHC class I expression in FRTL-5 cells at transcriptional level. Eur J Immunol 2000; 30:778–86.
[17] Baumann CA, Badamchian M, Goldstein AL. Thymosin alpha 1 is a time and dose-dependent antagonist of dexamethasome-induced apoptosis of murine thymocytes in vitro. Int J Immunopharmacol. 2000;22(12):1057-66.
[18] Palmer DB. The effect of age on thymic function. Front Immunol. 2013;4:316.
[19] Ershler WB, Gravenstein S, Geloo ZS. Thymosin alpha 1 as an adjunct to influenza vaccination in the elderly. Ann NY Acad Sci. 2007;1112:375-84.
[20] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com