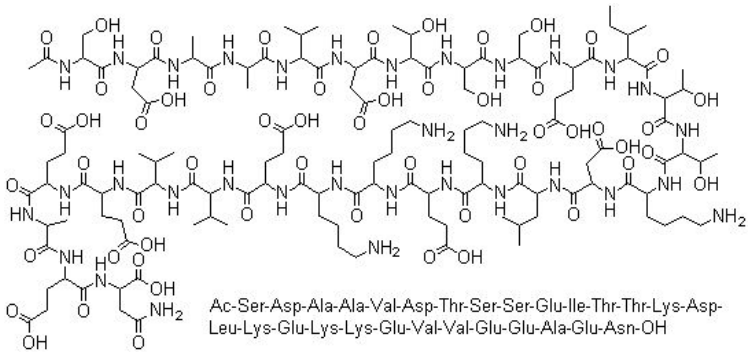
Professional Monograph

Thymosin alpha 1



INDICATION and USAGE SUMMARY

- Thymosin alpha-1 is a synthetic thymic peptide
- Modulates innate immunity (pleiotropic)[1,2,3]
    - Improves Th1 immune responses and helps balance Th1/Th2
    - 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
    - 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

[1] 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.
[2] 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.
[3] 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.

- Used for clinical conditions where immune support is necessary
    - Conditions requiring immune response modulation
    - 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
    - Geriatric immune support
    - DiGeorge's syndrome
- May reduce hematological toxicity of cytotoxic drug therapies
    - Cyclophosphamide
    - 5-fluorouracil (5FU)
    - Dacarbazine
    - Ifosfamide
- Zadaxin™ – proprietary thymosin alpha 1 (thymalfasin) approved in 30 countries for hepatitis B and C and cancer.[4,5]
    - Phase II clinical trials US – Hepatitis B
    - Phase III clinical trials US – Hepatitis C
    - Indicated as a monotherapy or combination therapy with interferon for the treatment of chronic hepatitis B, hepatitis C and cancer.[6]
    - Also indicated for treatment of non-small cell lung cancer (NSCLC), hepatocellular carcinoma, AIDS and malignant melanoma.[7,8]
    - General 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

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

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

Molar Weight: 3108.28 g/mol

Dosage Route: SubQ injection

[4] Wu X, Jia J, You H. Tymosin apha 1 treatment in chronic hepatitis B. Expert Opin Bil Ther. 2015;15 Suppl 1:S129-32.
[5] Kim BH, Lee YJ, Kim W, et al. Efficacy of thymosin alpha 1 plus peginterferon alpha-2 combination therapy compared with peginterferon alpha 2a monotherapy in HBeQG-positive chronic hepatitis B: a prospective multicenter randomized openlabel study. Scand J Gastroenterol. 2012;47(8-9):1048-55.
[6] Naylor PH. Zadaxin (thymosin alpha 1) for the treatment of viral hepatitis. Expert Opin Investig Drugs. 1999;8(3):281-7.
[7] Billich A. Thymosin alpha 21. SciClone Pharmaceuticals. Curr Opin Investig Drugs. 2002;3(5):698-707.
[8] 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.

Rapidly absorbed, peak serum within 2 hours, 2 hour half-life

Dosage:

- SubQ General Dosage
  - 1.5 mg SubQ every 3rd 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 twice weekly for 6-12 months

Overview

Thymosin alpha 1 is peptide containing 28 amino acid residues that are N-terminally acetylated and proteolytically processed from prothymosin alpha.[9] Thymosin alpha 1was isolated by Goldstein and coworkers from thymosin fraction 5, a mixture of peptides from calf thymus in the 1970s.[10] It is used to improve immune responses in times of need.[11]

Ta1 is pleiotropic – improves innate immunity when needed, down regulates immunity when not needed.[12] Ta1 is a thymic peptide that demonstrates a profound ability to restore immune system homeostasis in different physiological and pathological conditions (i.e., viral infections, cancer, immunodeficiency, vaccination support and immumosenescence) acting as multitasking protein depending on the host state of inflammation or immune dysfunction.[13]

Thymosin alpha 1 helps the body induce effective host-derived immune effectors and balance the Th1 / Th2 arms of immunity.[14] 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.[15] Additionally, Ta1 down-regulates the activity of terminal deoxynucleotide transferase (TdT) in TdT1 thymocytes, suggesting a role

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[9] Haritos AA, Goodall GJ, Horecker BL. Prothymosin alpha: isolation and properties of the major immunoreactive form of thymosin alpha 1 in rat thymus. Proc Natl Acad Sci U S A. 1984; 81: 1008-1011.
[10] Goldstein AL. History of the discovery of the thymosins Ann N Y Acad Sci. 2007;1112: 1– 13.
[11] Goldstein AL. History of the discovery of the thymosins Ann N Y Acad Sci. 2007;1112: 1– 13.
[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] 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.
[15] 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.

for Ta1 in thymocyte maturation. Ta1 has also been found to antagonize both activation induced (anti-CD3) and glucocorticoid-induced thymocyte apoptosis.[16] It has also been reoprted 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.[17] 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.[18]

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).[19]

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.[20] Zadaxin is currently in Phase III trials for the treatment of hepatitis C and in Phase II trials for hepatitis B in the US.

Hepatitis B - Zadaxin[21]

[16] 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.
[17] Palmer DB. The effect of age on thymic function. Front Immunol. 2013;4:316.
[18] 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.
[19] 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.
[20] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com
[21] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com

ZADAXIN thymosin alpha 1 (thymalfasin) is indicated as a monotherapy or combination therapy with interferon for the treatment of chronic hepatitis B. Pooled analysis of 3 randomized controlled trials comprising 223 patients was performed.[22] Thymosin alpha 1 was administered twice weekly for 6 months. Follow-up assessments were performed at 12 months after completion of treatment (see table 1 below). In multiple studies, ZADAXIN was reported to have a delayed therapeutic response 12 months or longer after completion of therapy.

Table 1: Efficacy of Thymosin alpha 1 Monotherapy for chronic hepatitis B

Study Reference	Number of Patients Treatment Groups	Response Rate at 12-months follow up*
US Phase 2 [1,5]	12 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 8 Placebo	(83%) Thymosin alpha 1 (25%) Placebo
US Phase 3 [2,5]	50 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 49 Placebo	(24%) Thymosin alpha 1 (12%) Placebo
Taiwan Phase 3 [3,4,5]	51 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 53 No treatment	(37%) Thymosin alpha 1 (25%) No treatment
Pooled Data [5]	113 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 110 Placebo or no treatment	(36%) Thymosin alpha 1 (19%) Placebo or no treatment
*Response rate is defined as the percentage of subjects who were HBV DNA and HBeAg negative at 12-months follow up		

Hepatitis C - Zadaxin[23]

ZADAXIN thymosin alpha 1 (thymalfasin) is indicated as a combination therapy with interferon for the treatment of chronic hepatitis C. Pooled analysis of 2 randomized controlled trials and 1 historical controlled trial comprising 121 ZADAXIN plus interferon, or interferon treated patients, was performed.[24] Thymosin alpha 1 was administered at least twice weekly for 6 to 12 months and interferon was administered up to three times weekly for 6 to 12 months. Follow-up assessments were performed upon completion of treatment and at 6 months after completion of treatment (see table 2 below).

[22] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com
[23] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com
[24] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com

Table 2: Efficacy of Thymosin alpha 1 therapy for Hepatitis C

Study Reference	Number of Patients Treatment Groups*	Response Rate at End of Treatment**	Sustained Response Rate***
US Phase 3 [6,9]	35 Thymosin alpha 1 + Interferon (Tα1 1.6 mg SQBIW 6 mos. + IFN 3 MU TIW 6 mos.)	ALT Response (37.1%) Thymosin alpha 1 + Interferon (16.2%) Interferon (2.7%) Placebo	ALT Response: (19.2%) Thymosin alpha 1 + Interferon (9.4%) Interferon
	37 Interferon (IFN 3 MU TIW 6 mos.)	Virologic Response (37.1%) Thymosin alpha 1	
	37 Placebo	+ Interferon (18.9%) Interferon (2.7%) Placebo	
Italy Phase 2 [7,9]	15 Thymosin alpha 1 (1.0 mg SQ qd for 4 days then BIW for 51 wks. + IFN 3 MU on day 4 then TIW for 51 wks.)	Virologic Response: (73.3%) Thymosin alpha 1 + Interferon	Virologic Response: (40.0%) Thymosin alpha 1 + Interferon
Italy Phase 2 [8,9]	17 Thymosin alpha 1 (1.6 mg SQ BIW for 6 mos. + +IFN 3 MU TIW 6 mos.) 17 Interferon	ALT Response: (70.6%) Thymosin alpha 1 + Interferon (35.3%) Interferon	ALT Response: (29.4%) Thymosin alpha 1 + Interferon (17.6%) Interferon
Pooled Data [9]	67 Thymosin alpha 1 (1.6 mg SQ BIW 6 to 12 mos. IFN 3 MU TIW 6 to 12 mos.) 54 Interferon	ALT Response: (44.7%) Thymosin alpha 1 + Interferon (22.2%) Interferon+	ALT Response: (22.4%) Thymosin alpha 1 + interferon (9.3%) Interferon++

*Intent-to-treat analysis
**ALT Response Rate is defined as the percentage of subjects who had normal ALT at end of treatment. Virologic Response Rate is defined as the percentage of subjects who were HCV RNA negative at end of treatment.
*** ALT Response Rate is defined as the percentage of subjects who had normal ALT at end of 6 months follow up Virologic Response Rate is defined as the percentage of subjects who were HCV RNA negative at end of 6 months follow up. US Phase 3 sustained response includes patients treated for 6 months and relapsers retreated for a total of 12 months.
+P=0.0096
++P=0.10

Cancer - Zadaxin[25]

ZADAXIN thymosin alpha 1 (thymalfasin) is indicated as a adjuvant therapy for chemotherapy-induced immune depression, immune insufficiency and immune suppression in patients with non-small cell lung carcinoma (NSCLC), malignant melanoma, hepatocellular carcinoma (HCC), breast cancer, non-Hodgkin's lymphoma (CHOP program), colorectal cancer, head and neck cancer, leukemia's, pancreatic carcinoma, and renal cell carcinoma. Clinical studies in over 1,000 patients with various types of cancer demonstrated that thymosin alpha 1 improved immunological parameters increased tumor response rates, and improved survival and quality of life (see table 3 for selected studies). Thymosin alpha 1 was either administered for 6 months or given between chemotherapy cycles for the duration of treatment.

Table 3: Efficacy of Thymosin alpha 1 therapy for Cancer

[25] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com

Study Reference	Number of Patients Treatment Groups	Clinical Outcome
Italy pilot study (HCC) [10]	12 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.)+TACE 12 TACE only	Statistically significant survival benefit and mprovement in immunological parameters in thymosin alpha 1 treated group compared with historical controls
US Phase 3 (NSCLC primarily Stage III) [11]	28 Thymosin alpha 1, 0.9 mg/m^2 SQ BIW up to 12 mos 13 placebo Thymosin alpha 1 treatment followed radiation therapy	Recurrence-free survival (p = 0.04) Greater effect in nonbulky vs. bulky tumors, p = 0.01 Median survival 52^+ vs. 32 wks Overall survival: p = 0.002
Italy Phase 2 (NSCLC, Stage II & IV) [12]	12 thymosin alpha 1, 1 mg SQ on days 8 to 11 and 15 to 18 + Ifosfamide + IFN-α3 MIU on days 11 and 18 10 Ifosfamide	Objective response: 66% vs. 10% Median time to progression: 18 wks vs. 9 wks (p = 0.0059) Median survival duration: 24 wks vs. 16 wks > 1 yr survival: 3 (35%) vs. 2 (20%) Lymphocyte count: maintained vs. decreased Hematologic toxicity reduced with no grade 3/4 toxicity compared to 50% in chemotherapy group
Italy Phase 2 (Malignant Melanoma) [13]	27 Thymosin alpha 1, 1 mg SQ on days 8 to 11 and 15 to 18 + DTIC + IFN-α Cycle repeated every 4 wks for 6 times (6 mos) or until disease progression	Overall response rate: 45% mean response duration: 13.5 mos
Italy Phase 2 (Malignant Melanoma) [14]	46 Thymosin alpha 2, mg s.c days 4-7 + DTIC + IL-2 Cycle repeated every 3 wks up to 6 times (app. 4 mos) Follow- up to 29 mos	Overall response rate: 36% Median time to progression: 5.5 mos Median survival: 11 mos (48% survived greater than 1 yr)

HIV/AIDS – Zadaxin[26]

Both preclinical and clinical studies have shown a high degree of immune restoration from the combined administration of Zadaxin and IFN α. Thus, Zadaxin in combination with AZT and IFN α is reported to improve outcomes for immune suppressed HIV-infected patients.

Potential Side Effects and/or Contraindications

- Thymosin alpha 1 peptide give subcutaneously is reported safe and efficacious in recommended dosages.
- Since 1979, thymosin alpha-1 is well tolerated. T α 1 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.[27,28,29,30]
- 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.

[26] Zadaxin Drug Monograph. SciClone Pharmaceuticals. www.Sciclone.com
[27] 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
[28] 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
[29] 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
[30] Zadaxin prescribing information SciClone Pharmaceuticals. www.scicloneinternational.com