ZADAXIN™

THYMOSIN ALFA 1, INJECTION
(THYMALFASIN)

DESCRIPTION

ZADAXIN™ thymosin alpha 1 (thymalfasin) for subcutaneous injection is a purified sterile lyophilized preparation of chemically synthesized thymosin alpha 1 identical to human thymosin alpha 1. Thymosin alpha 1 is an acetylated polypeptide with the following 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, and having a molecular weight of 3,108 daltons. The lyophilized preparation contains 1.6 mg thymosin alpha 1, 50 mg mannitol, and sodium phosphate buffer to adjust the pH to 6.8.

Product for Injection: Prior to administration, the lyophilized powder is to be reconstituted with 1 ml of the provided diluent (sterile water for injection). After reconstitution, the final concentration of ZADAXIN is 1.6 mg/ml.

CLINICAL PHARMACOLOGY

Preclinical Pharmacology : The mechanism of action of ZADAXIN is not completely understood but is thought to be related to its immunomodulating activities, centered primarily around augmentation of T-cell function. In various *in vitro* assays, thymosin alpha 1 has been shown to promote T-cell differentiation and maturation; for example, CD4+, CD8+, and CD3+ cells have all been shown to be increased. Thymosin alpha 1 has also been shown to increase production of IFN-γ, IL-2, IL-3, and expression of IL-2 receptor following activation by mitogens or antigens, increase NK cell activity, increase production of migratory inhibitory factor (MIF), and increase antibody response to T-cell dependent antigens. Thymosin alpha 1 has also been shown to antagonize dexamethasone-induced apoptosis of thymocytes *in vitro*. *In vivo* administration of thymosin alpha 1 to animals immunosuppressed by chemotherapy, tumor burden, or irradiation showed that thymosin alpha 1 protects against cytotoxic damage to bone marrow, tumor progression and opportunistic infections, thereby increasing survival time and number of survivors. Many of the *in vitro* and *in vivo* effects of thymosin alpha 1 have been interpreted as influences on either differentiation of pluripotent stem cells to thymocytes or activation of thymocytes into activated T-cells.

Pharmacokinetics: The pharmacokinetics of thymosin alpha 1 were studied in adult volunteers at single subcutaneous doses ranging from 0.8 to 6.4 mg and in multiple dose studies of 5 to 7 days duration at subcutaneous doses ranging from 1.6 to 16 mg. Thymosin alpha 1 was rapidly absorbed with peak serum levels achieved at approximately 2 hours. A dose proportional increase was seen in serum levels for C_{max} and AUC, and serum levels returned to basal levels by 24 hours after administration. The serum half-life was approximately 2 hours and there was no evidence of accumulation following multiple subcutaneous doses. Urine excretion ranged from 31% to 60% of the administered dose following single and multiple doses.

INDICATIONS AND USAGE

Chronic Hepatitis B: 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. Thymosin alpha 1 was administered twice weekly for 6 months. Follow-up assessments were performed at 12 months after completion of treatment (see table). In multiple studies, ZADAXIN was shown to have a delayed therapeutic response 12 months or longer after completion of therapy. A transient increase in ALT to more than twice baseline value (flare) can occur during ZADAXIN therapy. When ALT flare occurs, ZADAXIN should generally be continued unless signs and symptoms of liver failure are observed.

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.

Chronic Hepatitis C: 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. 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).

Pooled intent-to-treat analysis demonstrated sustained biochemical (ALT) response, defined as normal ALT 6 to 12 months after completion of treatment, observed in 22.4% of patients treated with combination therapy compared to 9.3% with interferon alone.

Efficacy of Thymosin Alpha 1 Combination Therapy with Interferon for Chronic 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 (Ta1 1.6 mg SQ BIW 6 mos. + IFN 3 MU TIW 6 mos.) 37 Interferon (IFN 3 MU TIW 6 mos.) 37 Placebo	ALT Response: (37.1%) Thymosin alpha 1 + Interferon (16.2%) Interferon (2.7%) Placebo Virologic Response: (37.1%) Thymosin alpha 1 + Interferon (18.9%) Interferon (2.7%) Placebo	ALT Response: (19.2%) Thymosin alpha 1 + Interferon (9.4%) Interferon
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 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 6-12 mos. + IFN 3 MU TIW 6-12 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 were ALT negative 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 were ALT negative 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

CONTRAINDICATIONS

ZADAXIN is contraindicated in patients with a history of hypersensitivity to thymosin alpha 1 or any component of the injection. Because ZADAXIN therapy appears to work by enhancing the immune system, it should be considered contraindicated in patients who are being deliberately immunosuppressed, such as organ transplant patients, unless the potential benefits of the therapy clearly outweigh the potential risks.

SciClone™
PHARMACEUTICALS

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(THYMALFASIN)

WARNINGS
None.

PRECAUTIONS
Information for Patients: Patients receiving ZADAXIN treatment should be directed in its use and informed of the benefits and risks associated with treatment. If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of syringes or needles. Patients should be instructed to store ZADAXIN refrigerated between 2^{O} and 8^{O}C (36^{O} to 46^{O} F). Reconstituted ZADAXIN should be used immediately.

Drug Interactions and Incompatibilities: Interactions between ZADAXIN and other drugs have not been fully evaluated. Caution should be exercised when administering ZADAXIN therapy in combination with other immunomodulating drugs. ZADAXIN should not be mixed with any other drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies with thymosin alpha 1 have not been done to determine carcinogenicity. Mutagenicity studies with thymosin alpha 1 showed no adverse findings.

Pregnancy Category C: Teratology studies in mice and rabbits have shown no difference in fetal abnormalities in control animals and animals given thymosin alpha 1. It is not known whether ZADAXIN can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. ZADAXIN should be given to a pregnant woman only if the benefits clearly outweigh the risks.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZADAXIN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness have not been established in patients below the age of 18 years.

ADVERSE REACTIONS
ZADAXIN is well tolerated. During clinical experience involving over 2000 individuals with various diseases distributed over all age groups, no clinically significant adverse reactions attributable to thymosin alpha 1 administration were reported (see table below).

Adverse experiences have been infrequent and mild, consisting primarily of local discomfort at the injection site, and rare instances of erythema, transient muscle atrophy, polyarthralgia combined with hand edema, and rash.

Disease		Adverse Event Rate
Viral Infection	Chronic hepatitis B Chronic hepatitis C Human immunodeficiency	<1% drug related adverse events for all indications
Cancer	Non-small cell lung cancer Melanoma	
Vaccine adjuvant	Hepatitis B vaccine Influenza vaccine	
Immune disorders	Autoimmune liver disease Primary immune deficiency	

OVERDOSAGE
There are no reported instances of deliberate or accidental overdosage in humans. Animal toxicology studies have shown no adverse reactions in single doses up to 20 mg/kg and in repeated doses up to 6 mg/kg/day for 13 weeks, which were the highest doses studied. The highest single dose tested in animals represents 800-times the clinical dose. Human studies have shown no adverse reactions at doses up to 16 mg biw for 4 weeks.

DOSAGE AND ADMINISTRATION
ZADAXIN is intended for subcutaneous injection and should not be given intravenously. It should be reconstituted with 1.0 ml of the diluent provided, which consists of 1.0 ml Sterile Water for Injection, immediately prior to use. At the discretion of the physician, the patient may be taught to self-administer the medication.

Chronic Hepatitis B: The recommended dose of ZADAXIN for chronic hepatitis B when used as a monotherapy or in combination with interferon (at the labeled dose and schedule for interferon) is 1.6 mg (900 μg/m^2) administered subcutaneously twice a week for 6 to 12 months. Patients weighing less than 40 kg should receive a ZADAXIN dose of 40 μg/kg.

Chronic Hepatitis C: The recommended dose of ZADAXIN for chronic hepatitis C when used in combination with interferon (at the labeled dose and schedule for interferon) is 1.6 mg (900 μg/m^2) administered subcutaneously twice a week for 12 months. Patients weighing less than 40 kg should receive a ZADAXIN dose of 40 μg/kg.

HOW SUPPLIED
ZADAXIN is supplied in single use vials containing 1.6 mg of lyophilized thymosin alpha 1 per vial. Each carton contains two vials of ZADAXIN. Each carton also contains two ampoules of diluent for ZADAXIN, each containing 1.0 ml of Sterile Water for Injection, which are to be used for reconstituting the ZADAXIN.

Store ZADAXIN between 2^{O} and 8^{O}C (36^{O} to 46^{O} F). Reconstituted ZADAXIN should be used immediately. ZADAXIN is demonstrated to be stable for at least 36 months from the date of manufacture when stored at 2-8°C.

ZADAXIN thymosin alpha 1 (thymalfasin) for injection is manufactured for SciClone Pharmaceuticals International Ltd., Hong Kong, by PATHEON Italia S.p.A., Monza, Italy. For further information, contact SciClone Pharmaceuticals International Ltd. in Hong Kong at +852-2-510-0118, or in Foster City, California, USA at +650-358-3456.

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