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.

Each vial of ZADAXIN thymosin alpha 1 contains 1.6 mg thymosin alpha 1, 50 mg mannitol, and sodium phosphate buffer to adjust the pH to 6.8.

Product for Injection

ZADAXIN is an acetylated polypeptide with the following sequence: Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-lle-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH. It has a molecular weight of 3,108 and a pl of 3.8.

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 augmenta-tion 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-y, 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 ALIC, 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

ZADAXIN is indicated for the treatment of chronic hepatitis B in patients 18 years of age or older with compensated liver disease and hepatitis B virus (HBV) replication (serum HBV DNA positive).

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 Placebo	(37%) Thymosin alpha 1 (25%) No Treatment
Pooled Data [5]	113 Thymosin alpha 1 (1.6 mg SQ BIW 6 mos.) 110 Placebo	(36%) Thymosin alpha 1 (19%) Placebo or No Treatment

***Response rate is defined as the percentage of subject who were HBV DNA and HBeAg negative at 12-months follow up.**

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.

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, for instance organ transplant patients, unless the potential benefits of the therapy clearly outweigh the potential risks.

WARNINGS

None.

PRECAUTIONS

Information for Patients

Patients receiving ZADAXIN treatment should be directed in its appropriate 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.

Laboratory Test: Liver function test, including serum ALT, albumin and bilirubin, should be evaluated periodically during treatment. HBeAg (Hepatitis B envelope antigen), HBsAg, HBV DNA and ALT should be evaluated at the end of treatment as well as 2, 4, and 6 months after treatment, since patients may become virologic responders during the 6 months following treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies with ZADAXIN have not been done to determine carcinogenicity.

Mutagenicity studies with ZADAXIN showed no adverse findings.

Pregnancy Category C
Animal reproduction studies in mice and rabbits have shown no difference in fetal abnormalities in control animals and animals given ZADAXIN. It is not known whether ZADAXIN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ZADAXIN should be given to a pregnant woman only if clearly needed.

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.

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 immune modulating drugs. ZADAXIN should not be mixed with any other drug.

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 (< 1% drug related adverse events).

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.

DOSAGE AND ADMINISTRATION
The recommended dose of ZADAXIN for the treatment of chronic hepatitis B is 1.6 mg administered subcutaneously twice a week with doses separated by 3 or 4 days. Therapy should be continued for six months (52 doses) without interruption. ZADAXIN should not be given intramuscularly or 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.

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.

HOW SUPPLIED
ZADAXIN is supplied in single use vials containing 1.6 mg of lyophilized thymosin alpha 1 per vial. It is available in cartons 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 for Injection.

Store ZADAXIN between 2° and 8°C (36° to 46° F). It should be used immediately after reconstitution. Shelf life is 3 years.

ZADAXIN, thymosin alpha 1 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.

References:

1. Mutchnick, M.G., Cummings, G.D., Hoofnagle, J.H., and D.A. Shafritz (1992) *Thymosin: An innovative approach to the treatment of chronic hepatitis B*, in Combination therapies. Biological Response Modifiers in the Treatment of Cancer and Infectious Diseases, A.L. Goldstein and E. Garaci, Editors. Plenum Publishing Corp: New York. p. 149-156.
2. Mutchnick, M.G., Lindsay, K.L., Schiff, E.R., Cummings, G.D., and H.D. Appelman (1995) *Thymosin alpha t treatment of chronic hepatitis B: a multi-center, randomized, placebo-controlled double blind study*. Gastroenterology 108(4): p. A1127.
3. Lee, S.-D., D.-S. Chen, and Y.-F. Liaw (1997) *Multicenter Study of Thymosin Alpha 1 in the Treatment of Chronic Hepatitis B*. Data on file.
4. Chien, R.-N., Liaw Y.-F., Chen, T.-c., Yeh, c.-T., and 1.-S. Sheen (1998) *Efficacy of Thymosin α1 at in Patients with Chronic Hepatitis B: A Randomized, Controlled Trial*. Hepatology 27 (5) May 1998: p.1383-1387.
5. Niedzwiecki, D., Luo, D., Finn, D.S., Whiting, G.W., Connelly, J.E., Kumashiro, M., Allen, I.E., and S.D. Ross (1997) *The efficacy of thymosin alpha 1 in chronic hepatitis B: a meta-analysis*, Data on file.

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