Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Actimmune (interferon gamma-1b)

- **BCBSKS will review Prior Authorization requests**

  Prior Authorization Form:
  http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf

  Link to Drug List (Formulary):
  http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: June 10, 2016
Revision Date(s): June 10, 2016
Current Effective Date: June 10, 2016

Institutional
Original Effective Date: June 10, 2016
Revision Date(s): June 10, 2016
Current Effective Date: June 10, 2016

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

ACTIMMUNE is a biologically manufactured protein called interferon gamma, that is similar to a protein your body makes naturally. In the body, interferon gamma is produced by cells of the immune system and helps to prevent serious infections.

ACTIMMUNE is approved by the US Food and Drug Administration to treat two conditions: Chronic Granulomatous Disease (CGD) and Severe, Malignant Osteopetrosis (SMO). In patients with Chronic Granulomatous Disease (CGD), *ACTIMMUNE* helps to lower the risk and severity of serious infections. In patients with Severe Malignant Osteopetrosis (SMO), *ACTIMMUNE* can slow the worsening of the disease.

Target Drug

- **Actimmune®** (interferon gamma-1b)

FDA Approved Indications and Dosage

ACTIMMUNE is indicated for:

- Reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD).
- Delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO).

The recommended dosage of *ACTIMMUNE* administered subcutaneously, for the treatment of patients with CGD and SMO is shown in Table 1 below:

Table 1
Recommended Dosage for ACTIMMUNE for the Treatment of Patients with CGD and SMO

Body Surface Area (m^2)	Dose (mcg/m^2)	Dose (International Units/m^2)[a]	Frequency
Greater than 0.5 m^2	50 mcg/m^2	1 million International Units/m^2	Three times weekly (for example: Monday, Wednesday and Friday)
Equal to or less than 0.5 m^2	1.5 mcg/kg/dose		Three times weekly (for example: Monday, Wednesday and Friday)

[a] Note that the above activity is expressed in International Units (1 million International Units/50 mcg). This is equivalent to what was previously expressed as units (1.5 million units/50 mcg).

POLICY

A. Actimmune (interferon gamma-1b) may be considered **medically necessary** when dosed as per the FDA approved recommended dosage (see Table 1 above) for:

1. Reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD)

2. Delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO)

B. Actimmune (interferon gamma-1b) is considered **experimental / investigational** for all other indications, including but not limited to idiopathic pulmonary fibrosis.

FDA Labeled Contraindications	
Agent	**Contraindications**
Actimmune (interferon gamma-1b)	In patients who develop or have known hypersensitivity to interferon-gamma*, E. coli* derived products, or any component of the product.

Contraindicated as Concomitant Therapy	
Actimmune (interferon gamma-1b)	▪ Concomitant use of drugs with neurotoxic, hematotoxic or cardiotoxic effects may increase the toxicity of interferons. ▪ Avoid simultaneous administration of *ACTIMMUNE* with other heterologous serum protein or immunological preparations (e.g., vaccines).

RATIONALE

ACTIMMUNE (Interferon gamma-1b), an interferon gamma, is a single-chain polypeptide containing 140 amino acids. Production of ACTIMMUNE is achieved by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the recombinant protein.

Interferons bind to specific cell surface receptors and initiate a sequence of intracellular events that lead to the transcription of interferon-stimulated genes. The three major groups of interferons (alpha, beta, gamma) have partially overlapping biological activities that include immunoregulation such as increased resistance to microbial pathogens and inhibition of cell proliferation. Type 1 interferons (alpha and beta) bind to the alpha / beta receptor. Interferon gamma binds to a different cell surface receptor and is classified as Type 2 interferon. Specific effects of interferon gamma include the enhancement of the oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity (ADCC), activation of natural killer(NK) cells, and the expression of Fc receptors and major histocompatibility antigens.

Chronic Granulomatous Disease (CGD) is an inherited disorder of leukocyte function caused by defects in the enzyme complex responsible for phagocyte superoxide generation. *ACTIMMUNE* does not increase phagocyte superoxide production even in treatment responders.

In severe, malignant osteopetrosis (SMO) (an inherited disorder characterized by an osteoclast defect, leading to bone overgrowth, and by deficient phagocyte oxidative metabolism), a treatment-related enhancement of superoxide production by phagocytes was observed. *ACTIMMUNE* was found to enhance osteoclast function *in vivo*.

In both disorders, the exact mechanism(s) by which *ACTIMMUNE* has a treatment effect has not been established. Changes in superoxide levels during *ACTIMMUNE* therapy do not predict efficiency and should not be used to assess patient responses to therapy.

Pharmacokinetics

Pharmacokinetic studies in patients with CGD have not been performed. The intravenous, intramuscular, and subcutaneous pharmacokinetics of *ACTIMMUNE* have been investigated in 24 healthy male subjects following single-dose administration of 100 mcg/m^2 (twice the recommended dose for CGD and SMO patients). *ACTIMUNE* is rapidly cleared after intravenous administration (1.4 liters/minute) and slowly absorbed after intramuscular or subcutaneous injection. After intramuscular or subcutaneous injection, the apparent fraction of dose absorbed was greater than 89%. The mean elimination half-life after intravenous administration of 100 mcg/m^2 in healthy male subjects was 38 minutes. The mean elimination half-lives for intramuscular and subcutaneous dosing with 100 mcg/m^2 were 2.9 and 5.9 hours, respectively. Peak plasma concentrations, determined by ELISA, occurred approximately 4 hours (1.5 ng/mL) after intramuscular dosing and 7 hours (0.6 ng/mL) after subcutaneous dosing. Multiple dose subcutaneous pharmacokinetic studies were conducted in 38 healthy male subjects. There was no accumulation of *ACTIMMUNE* after 12 consecutive daily injections of 100 mcg/m^2.

Interferon gamma was not detected in the urine of healthy human volunteers following administration of 100 mcg/m^2 of *ACTIMMUNE* by the intravenous, intramuscular and subcutaneous routes. *In vitro* perfusion studies utilizing rabbit livers and kidneys demonstrate that these organs are capable of clearing interferon gamma from perfusate.
Studies of the administration of interferon-gamma to nephrectomized mice and squirrel monkeys demonstrate a reduction in clearance of interferon-gamma from blood; however, prior nephrectomy did not prevent elimination.

Clinical Studies

Effects in Chronic Granulomatous Disease (CGD)

A randomized, double-blind, placebo-controlled trial of *ACTIMMUNE* (interferon gamma-1b) in patients with Chronic Granulomatous Disease (CGD), was performed to determine whether *ACTIMMUNE* administered subcutaneously on a three times weekly schedule could decrease the incidence of serious infectious episodes and improve existing infectious and inflammatory conditions in patients with CGD. One hundred twenty-eight eligible patients were enrolled in this trial including patients with different patterns of inheritance. Most patients received prophylactic antibiotics. Patients ranged in age from 1 to 44 years with the mean age being 14.6 years. The study was terminated early following demonstration of a highly statistically significant benefit of *ACTIMMUNE* therapy compared to placebo with respect to time to serious infection (p=0.0036),

the primary endpoint of the investigation. Serious infection was defined as a clinical event requiring hospitalization and the use of parenteral antibiotics.

The final analysis provided further support for the primary endpoint (p=0.0006). There was a 67 percent reduction in relative risk of serious infection in patients receiving *ACTIMMUNE* (n=63) compared to placebo (n=65). Additional supportive evidence of treatment benefit included a twofold reduction in the number of primary serious infections in the *ACTIMMUNE* group (30 on placebo versus 14 on *ACTIMMUNE*, p=0.002) and the total number and rate of serious infections including recurrent events (56 on placebo versus 20 on *ACTIMMUNE*, p=<0.0001). Moreover, the length of hospitalization for the treatment of all clinical events provided evidence highly supportive of an *ACTIMMUNE* treatment benefit. Placebo patients required three times as many inpatient hospitalization days for treatment of clinical events compared to patients receiving *ACTIMMUNE* (1493 versus 497 total days, p=0.02). An *ACTIMMUNE* treatment benefit with respect to time to serious infection was consistently demonstrated in all subgroup analyses according to stratification factors, including pattern of inheritance, use of prophylactic antibiotics, as well as age. There was a 67 percent reduction in relative risk of serious infection in patients receiving *ACTIMMUNE* compared to placebo across all groups. The beneficial effect of *ACTIMMUNE* therapy was observed throughout the entire study, in which the mean duration of *ACTIMMUNE* administration was 8.9 months/patient.

Effects In Severe, Malignant Osteopetrosis (SMO)

A controlled, randomized study in patients with severe, malignant osteopetrosis (SMO) was conducted with *ACTIMMUNE* administered subcutaneously three times weekly. Sixteen patients were randomized to receive either *ACTIMMUNE* plus calcitriol (n=11), or calcitriol alone (n=5). Patients ranged in age from 1 month to 8 years, mean 1.5 years. Treatment failure was considered to be disease progression as defined by 1) death, 2) significant reduction in hemoglobin or platelet counts, 3) a serious bacterial infection requiring antibiotics, or 4) a 50 dB decrease in hearing or progressive optic atrophy. The median time to disease progression was significantly delayed in the *ACTIMMUNE* plus calcitriol arm versus calcitriol alone. In the treatment arm, the median was not reached. Based on the observed data, however, the median time to progression in this arm was at least 165 days versus the median of 65 days in the calcitriol alone arm. In an analysis which combined data from a second study, 19 of 24 patients treated with *ACTIMMUNE* plus or minus calcitriol for at least 6 months had reduced trabecular bone volume compared to baseline.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9216	Injection interferon, gamma-1b, 3 million units

DIAGNOSES

D71	Functional disorders of polymorphonuclear neutrophils
J84.122	Idiopathic pulmonary fibrosis
Q78.2	Osteopetrosis

REVISIONS

06-10-2016	Policy published 05-11-2016. Policy effective 06-10-2016.
	Policy added to the bcbsks.com web site.

REFERENCES

1. Actimmune prescribing information. Horizon Pharma Ireland Ltd. Dublin, Ireland. U.S. License No. 2022. Distributed by: HZNP USA Inc. Roswell, GA 30076. Available on-line at: http://www.actimmune.com/pdf/10889_Actimmune-PI_8_5x11.pdf . Accessed March 2016.
2. Actimmune Website http://www.actimmune.com/