Interferon Gamma-1B (Actimmune®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO238

Description

Interferon Gamma-1B (Actimmune®) is a subcutaneously administered medication which works through an unknown mechanism of action after binding to the cell's surface. The three major groups of interferons (alpha, beta, gamma) all have overlapping properties. Interferon gamma binds to a different surface receptor than alpha and beta and is considered a Type 2 interferon. Specific effects from using interferon gamma include activation of natural killer (NK) cells, enhancement of the oxidative metabolism of macrophages, and antibody dependent cellular cytotoxicity (ADCC).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Interferon Gamma-1B (Actimmune®)	100mcg (2 million IU)/0.5ml vial	Severe Malignant Osteopetrosis (SMO); Chronic Granulomatous Disease (CGD)	BSA* **over** 0.5 m^2: 50mcg/m^2 Three times weekly
			BSA* **equal to or less than** 0.5m^2: 1.5mg/kg/dose Three times weekly

**maximum dose: 50mcg/m^2 Body surface area (BSA*

Initial Evaluation

I. **Interferon Gamma-1B (Actimmune)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a specialist (e.g., endocrinologist, immunologist, geneticist); **AND**
   B. Member will not use this medication in combination with another biologic or other non-biologic specialty medication; **AND**
   C. A diagnosis of one of the following:
      1. **Chronic granulomatous disease (CGD)**; **AND**
         i. Attestation the member has a confirmed molecular genetic test and/or by neutrophil-functioning test confirming diagnosis; **AND**

ii. Member is on continuous daily antibiotic therapy (e.g., sulfamethoxazole-trimethoprim) and antifungal therapy (e.g., itraconazole) for infection prophylaxis; **OR**

2. **Severe Malignant Osteopetrosis (SMO)**; **AND**
   i. Member has confirmed genetic testing identifying a mutation linked to severe, infantile, malignant osteopetrosis; **AND**
   ii. Member has had a radiographic (x-ray) image confirming skeletal features related to osteopetrosis

II. **Interferon Gamma-1B (Actimmune)** is considered investigational when used for all other conditions, including but not limited to:
   A. Atopic Dermatitis
   B. Renal Cell Carcinoma
   C. Mycosis Fungoides/Sezary Syndrome
   D. Friedreich's Ataxia
   E. Noninfantile osteopetrosis (conditions outside of severe, infantile (SMO))

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in primary infections, stabilization of platelet or hemoglobin counts, decrease/stabilization in optic atrophy]

Supporting Evidence

I. Chronic granulomatous disease (CGD) is a rare and inherited primary immune deficiency disorder affecting white blood cells and the body's ability to resist infections caused by certain types of bacterial and fungal species. Overtime, this causes the body to develop chronic inflammation of the tissues, known as granulomas, which can be widely distributed over the body and have the potential to develop into life-threatening infections of the skin, lungs, and bones.
II. In CGD, there is a genetic mutation in one of five genes that cause a defect in an enzyme called phagocyte NADPH oxidase; this enzyme is used by certain white blood cells in the cell killing process of certain bacteria and fungi. Usually this is routinely done in children with a family history of CGD or will be performed in children who have symptoms that match the symptom

profile. The first testing done is either the DHR (dihydrorhodamine) (flow cytometry test) or the NBT (nitroblue tetrazolium) test. Both work in a similar manner and check to see if the patient's blood cells are producing the enzyme NADPH oxidase. The DHR test will change the fluorescein of dihydrorhodamine and that can be detected by the flow cytometer; the NBT test will change the color of the cell itself and this can be then seen under a microscope. Once a positive result is found on either test, genetic testing is done to assess which mutation the patient has, as the type of mutation can impact how the disease might present and when it might present (i.e. later in life in certain carriers; more autoimmune manifestations like Raynaud's, oral ulcers) and this genetic testing is important for carriers to know the genetic potential of passing to any children they might have.

III. As CGD is a genetic disease, the first symptoms are usually noticed during infancy or childhood, though cases have been reported not diagnosed until the early teens or even adulthood. Standard of care consists of continuous antibiotic therapy to help prevent infections, such as trimethoprim/sulfamethoxazole to prevent bacterial infections and itraconazole for anti-fungal protection. Corticosteroids are also helpful for treating granulomatous complications and to bring down inflammation. The only potential cure for CGD is a bone marrow transplant which has been successful in some patients. Interferon gamma-1B has been shown in vitro and in vivo to correct parts of the damage to the oxidative metabolic system of the cells and therefore, help improvement their microbe killing potential (ability to kills bacteria, fungi, and viruses).

IV. Actimmune was approved by the FDA for use in CGD following a randomized, double blind, placebo-controlled trial to determine if Actimmune used subcutaneously (SQ) three times a week could decrease the incidence of serious infectious episodes and improve existing infectious and inflammatory conditions of those enrolled in the study with CGD. A hundred and twenty-eight patients were enrolled, of those enrolled all had different methods of genetic inheritance and most patients were on prophylactic antibiotics. Patients had a median age of 14.6 years but ranged from 1-44 years. The study itself ended early following demonstration of a highly statistically significant benefit of Actimmune compared to placebo, (p=0.0036) for the primary endpoint of the study, time to a serious infection. There was a 67% reduction in relative risk of serious infections in those receiving Actimmune to place (N=63 to N=65, respectively) and additional evidence for the treatment benefit of Actimmune showed a twofold reduction in the number of primary infections (30, placebo and 14, Actimmune; p=0.002).

V. Osteopetrosis is a genetic disease marked by increased bone density from a defect in the bone being reabsorbed into the cells by osteoclasts. This leads to bone being made up/built of a defective structure causing them to be brittle and likely to fracture; this often leads to misclassification under a type of bone fragility. Three types of osteopetrosis exist and are differentiated based on the genetic mutation. The autosomal recessive form, severe malignant osteopetrosis (SMO) [sometimes referred to as malignant infantile osteoporosis (MIOP)], is apparent soon after birth and shortens life expectancy, usually leading to death within the first decade of life, affecting about 1 in 250,000 people. Genetic testing is recommended once an x-

ray diagnosis is established because it can separate the different forms of osteopetrosis and provide meaningful effect on management strategies.

VI. Additional types of osteopetrosis are Autosomal Dominant (aka Albers-Schonberg disease or ADO), Intermediate Autosomal (IAO), and Adult Delayed-Onset. ADO is the most common and usually has an onset in adolescence or adulthood with long bone involvement leading to fractures along these bones such as the femur and ulnar. Other common symptoms include hip osteoarthritis, scoliosis, osteomyelitis of the jawbone, and infection within the bone itself. IAO onsets in childhood and can cause skeletal changes as well as visual impairment from optic nerve compression but does not change life expectancy. Adult Delayed-Onset is a milder type of ADO with normal bone structure at birth and people tend to remain asymptomatic. In this later state, bone mass will increase with age, and usually osteomyelitis of the jaw is first symptom, followed by bone pain, fractures, back pain (along vertebra), and degenerative arthritis.

VII. The only established cure for SMO is a hematopoietic stem cell transplant (HSCT) which allows restoration of bone resorption by the donor osteoclasts. Certain genetic mutations within SMO will not benefit from the transplant (those with the *RANKL* gene) and a large number of patients develop some sort of progression neurodegeneration which is not helped with a HSCT. For patients where an HSCT is not appropriate, corticosteroids may be considered, but there is not strong evidence to support their routine use. Interferon Gamma-1B was approved to help delay disease progression along with dietary and nutrition support. Interferon Gamma-1B is not indicated for the other types of osteopetrosis as ADO, IAO, or Adult-Delayed; as they can all be managed by things such as calcitriol, to help stimulate osteoclasts, erythropoietin, or corticosteroids.

VIII. Actimmune received FDA approval for SMO following a randomized, controlled trial in patients with SMO who received doses of Actimmune (three times weekly) + calcitriol or just calcitriol alone. The study only enrolled 16 patients with n=11 receiving study regime and n=5 receiving the controller alone; patients were a mean age of 1.5 years (1month-8 years). The study evaluated time to disease progression and treatment failure was considered to be disease progression based on four outcomes: 1. Death; 2. Significant reductions in hemoglobin or platelet counts; 3. Serious bacterial infections requiring antibiotics; or 4. A 50dB decrease in hearing or progressive optic atrophy. The median time to disease progression was significantly delayed in the study arm versus control arm. However, this was based on the observed data as time to progression in the treatment arm was at least 165 days versus 65 days in the calcitriol alone arm.

IX. Actimmune has a similar safety profile as the other interferons. The most common adverse reactions include fever, headache, chills, myalgia, or fatigue. It is recommended to have baseline hematology, blood chemistries, and urinalysis prior to starting and at 3-month intervals once using the medication. It is further recommended for severe reactions, to dose reduce by 50% or discontinue the therapy until the ADE resolves. Examples of these serious adverse reactions are

neutropenia, thrombocytopenia, elevations of AST/ALT, decreased mental status, and gait disturbances.

X. As each of these FDA label indications are an involved genetic disorder, the request should be coming from a specialist with understanding of the disease state.

Investigational or Not Medically Necessary Uses

I. Interferon Gamma-1B (Actimmune) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Atopic Dermatitis (AD)
      i. In 2000, a randomized, placebo-controlled study looked at the therapeutic effect of two different dosages of interferon gamma for AD for therapeutic efficacy. Fifty-one patients with severe recalcitrant AD were treated with interferon gamma (20 patients at low dose and 21 patients at high dose) SQ 3 x weekly for 12 weeks. Both groups reached treatment goals compared to placebo with statistical significance ($p<0.05$) and the higher dose showed more rapid improvement. The conclusion of the study was that interferon gamma was safe and effective for AD. Since then, there have been 6 other clinical trials, with largest enrolling 51 patients and the longest lasting 24 weeks, all noting improvement. Currently, this indication is considered experimental and investigational due to the lack of larger scale clinical trials or head-to-head clinical trials; coupled with the approval of the gold standard biologics such as Dupixent, for treatment of AD which occurred after the 2016 review article was published.
   B. Renal Cell Carcinoma
      i. A multicenter, randomized, placebo-controlled, double-blind trial for metastatic renal cell carcinoma was completed in 1999/2000. This trial enrolled 197 patients to receive either placebo or recombinant interferon gamma-1b (60 mcg/m2) SQ every 7 days until disease progression. There was no statistical significance ($p=0.75$) for the 95% confidence interval of overall response rate of interferon gamma-1b of 4% (1.4-11.5) to placebo of 6% (2.5-13.2). The study concluded with a statement that the lack of efficacy in this trial shows the importance of continued research in this field.
   C. Mycosis Fungoides/Sezary Syndrome
      i. Support for this experimental use is supported by the National Comprehensive Cancer Network (NCCN) guidelines for Primary Cutaneous Lymphomas as level of evidence 2a. The trial used in the supporting evidence is from the late 1980s/early 1990s; the phase II trial had a total of 16 patients enrolled with various stages of cutaneous T-cell lymphomas (CTCL). Five patients had partial response with a

median response of 10 months, and 6 others showed minor or mixed response. The trial suggested that interferon gamma has efficacy in the treatment of CTCL refractory to use interferon alpha (as being on another interferon was allowed by study design). The quality of this evidence is considered low at this time given the open label trial design, small sample size, and lack of comparator arm.

D. Friederichs's Ataxia
   i. In 2016, Horizon Pharma launched a phase 3 trial, STEADFAST, to evaluate Actimmune for the treatment of Friederichs's Ataxia (FA). The study's primary endpoint was a change from baseline in the modified Friedreich's Ataxia Rating Scale at 26 weeks versus treatment with placebo. The scale is an exam-based rating scale that measuring progression using parameters such as speech, ability to swallow, upper and lower limb coordination, gait, and posture. The trial did not meet statistically significant to this end point or the secondary end points and was stopped prior to original end date due to this finding.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	10/2021