Interferon Gamma-1b

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Related Coverage Resources
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Medical Necessity Criteria

This coverage policy addresses the use of interferon gamma-1b (Actimmune) for non-oncology indications. The use of interferon gamma-1b (Actimmune) for oncology indications is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Oncology Medications).

I. Interferon gamma-1b (Actimmune®) is considered medically necessary for Chronic Granulomatous Disease if BOTH of the following criteria are met:
   • Diagnosis documented by molecular genetic test identifying a gene-related mutation linked to chronic granulomatous disease (for example, biallelic pathogenic variants in CYBA, NCF1, NCF2, and NCF4 cause autosomal recessive CGD; mutation of CYBB causes X-linked CGD)
   • Prescribed by, or in consultation with a physician who specializes in Chronic Granulomatous Disease (for example, geneticist, immunologist)

II. Interferon gamma-1b (Actimmune®) is considered medically necessary for Severe Malignant Osteopetrosis (SMO) when BOTH of the following criteria are met:
   • Diagnosis documented by ONE of the following:
     o Individual has had a radiographic (X-ray) imaging report demonstrating skeletal features related to osteopetrosis (for example, increased bone density, diffuse and focal sclerosis of varying severity, modelling defects at metaphyses)
Individual has had a molecular genetic test identifying a gene-related mutation linked to malignant osteopetrosis, severe infantile (for example, biallelic pathogenic variants in TCIRG, CLCN7, OSTM1, RANKL, or RANK)

- Prescribed by, or in consultation with a physician who specializes in Severe Malignant Osteopetrosis (SMO) (for example, geneticist, endocrinologist)

Initial and reauthorization is up to 12 months unless otherwise stated.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy as applicable.

Interferon gamma-1b (Actimmune) is considered experimental, investigational or unproven for any other use.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

**FDA Approved Indications**

**FDA Approved Indication**
Actimmune is indicated for reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD).

Actimmune is indicated for delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO).

**Recommended Dosing**

**FDA Recommended Dosing**
Recommended Dosage for Actimmune for the Treatment of Patients with CGD and SMO

<table>
<thead>
<tr>
<th>Body Surface Area (m2)</th>
<th>Dose (mcg/m2)</th>
<th>Dose (International Units/m2)*</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 0.5 m2</td>
<td>50 mcg/m2</td>
<td>1 million International Units/m2</td>
<td>Three times weekly (For example, Monday, Wednesday and Friday)</td>
</tr>
<tr>
<td>Equal to or less than 0.5 m2</td>
<td>1.5 mcg/kg/dose</td>
<td>------------</td>
<td>Three times weekly (For example, Monday, Wednesday and Friday)</td>
</tr>
</tbody>
</table>

* 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).

**Drug Availability**
Each single use 0.5 mL of Actimmune contains: 100 mcg (2 million International Units) of interferon gamma-1b.

**Background**

**Disease Overview**
**Chronic Granulomatous Disease**
CGD is an inherited primary immunodeficiency caused by functional impairment of the dihydronicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in neutrophilic granulocytes and monocytes characterized by recurrent and severe infections, dysregulated inflammation, and autoimmunity. (Arnold, 2017) CGD may present any time from infancy to late adulthood; however, the vast majority of affected individuals are diagnosed before age five years. (Genetic Testing Registry, 2019) Mutations in the CYBA, CYBB, NCF1, NCF2, or NCF4 gene can cause CGD.
**Severe, Malignant Osteopetrosis**

SMO is an inherited disorder characterized by an osteoclast defect, leading to bone density overgrowth, and by deficient phagocyte oxidative metabolism. This leads to accumulation of bone with defective structure, making them brittle and susceptible to fracture. In some cases, this is also accompanied by skeletal abnormalities. (Stark, 2009) About thirty percent of all cases of osteopetrosis the cause of the condition is unknown, however, nine gene-related mutations are associated with osteopetrosis (CA2, CLCN7, IKBKG, ITGB3, OSTM1, PLEKHM1, TCIRG1, TNFRSF11A, TNFSF11). (Genetics Home Reference/NIH, 2019)

In both disorders, the exact mechanism(s) of Actimmune’s treatment effect has not been established. Changes in superoxide levels during Actimmune therapy do not predict efficacy and should not be used to assess patient response to therapy. (Actimmune Prescribing Information, 2017)

**Professional Societies/Organizations**

**Chronic Granulomatous Disease**

**American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma & Immunology**

The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) have jointly accepted responsibility for establishing the practice parameter for the diagnosis and management of primary immunodeficiency. (Bonilla, 2015) Screening for CGD should include direct measurement of superoxide production (nitroblue tetrazolium reduction test [NBT] or dihydrorhodamine 123 [DHR] oxidation test) confirmed with testing for genetic mutation in the genes that make up the NADPH. (Yu, 2018) Neutrophils from a small sample of peripheral blood are activated to produce superoxide which is detected by the NBT, which is converted from a yellow water-soluble compound to a dark-blue insoluble formazan that can be clearly detected microscopically. Activation of neutrophils with phorbol myristate acetate results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD. Summary statement 152 of the practice parameter discusses that phagocyte oxidase activity measurement should be the first screening test for CGD. Then further details that the screening diagnostic tests rely on various measures of neutrophil superoxide production and include: direct measurement of superoxide production, the nitroblue tetrazolium reduction test, and the dihydrorhodamine 123 (DHR) oxidation test. DHR test relies on the ability of phagocytes on stimulation to oxidize the dye for DHR to a green fluorescent molecule by the superoxide that is generated. Therefore, this type of fluorescence is measured by flow cytometry and therefore objective and quantitative. On the other hand, nitroblue tetrazolium test relies on visual scoring and is therefore, qualitative and highly subjective with an increased rate of results that are false-negative. The practice parameter states that the ultimate confirmation is done by genetic mutation testing in the genes that make up the NADPH (gp91phox, p22phox, p47phox, p67phox, and p40phox). Summary statement 153 of the practice parameter recommends patients with CGD be given prophylaxis with antimicrobial agents and Actimmune.

**Severe, Malignant Osteopetrosis**

**Osteopetrosis Working Group Consensus Guidelines**

The Osteopetrosis Working Group developed expert consensus guidelines for the diagnosis and management of osteopetrosis. (Wu, 2017) The guidelines recommend diagnosis is determined by classic radiographic (X-ray) features of osteopetrosis followed up by genetic testing to differentiate between the different forms of osteopetrosis with unique complications. The guidelines suggests the use of Actimmune to be considered experimental in noninfantile osteopetrosis with limited clinical experience. Furthermore, acknowledging the FDA indication for SMO and advising the indication pertains only to severe infantile osteopetrosis.

**Off label uses:**

AHFS Drug Information 2019 Edition supports no off-label uses of interferon gamma-1b.

**References**

1. Actimmune® subcutaneous injection [prescribing information]. Lake Forest, IL: Horizon Pharma USA; May 2017