Effective Date **9/1/2022**
Next Review Date… **9/1/2023**
Coverage Policy Number **IP0201**

Interferon Gamma-1b for Non-Oncology Uses

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for 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).

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

Medical Necessity Criteria

Interferon gamma-1b (Actimmune) is considered medically necessary when ONE of the following is met (1 or 2):

1. **Chronic Granulomatous Disease.** Individual meets **BOTH** of the following criteria (A and B):

A. Documented diagnosis confirmed by a molecular genetic test identifying variants linked to chronic granulomatous disease (for example, biallelic pathogenic variants in *CYBA, NCF1*, *NCF2,* and *NCF4* cause autosomal recessive CGD; pathogenic variants in *CYBB* cause X-linked CGD)
B. The medication is prescribed by, or in consultation with, a medical geneticist, immunologist, or physician who specializes in chronic granulomatous disease

2. **Severe Malignant Osteopetrosis, Infantile.** Individual meets **BOTH** of the following criteria (A and B):
   A. Documented diagnosis confirmed by **ONE** of the following (i or ii):
      i. Individual has had radiographic (X-ray) imaging demonstrating skeletal features related to osteopetrosis (for example, increased bone density, diffuse and focal sclerosis of varying severity, modelling defects at metaphyses)
      ii. Individual has had a molecular genetic test identifying variants linked to severe, infantile malignant osteopetrosis (for example, biallelic pathogenic variants in *CA2, CLCN7, IKBKG, ITGB3, OSTM1, PLEKHM1, RANKL, RANK, TCIRG1, TNFRSF11A,* or *TNFSF11*)
   B. The medication is prescribed by, or in consultation with, an endocrinologist, geneticist, or physician who specializes in severe malignant osteopetrosis

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.

Reauthorization Criteria

Interferon gamma-1b (Actimmune) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven.

Background

OVERVIEW
Actimmune, an interferon gamma, is indicated for the following uses:[1]

- Chronic granulomatous disease (CGD), to reduce the frequency and severity of serious infections.
- Severe, malignant osteopetrosis (SMO), to delay time to disease progression.

In both disorders, the exact mechanism(s) of Actimmune's treatment effect have 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.

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

Body Surface Area (m2)	Dose (mcg/m2)	Dose (International Units/m2)[a]	Frequency
Greater than 0.5 m2	50 mcg/m2	1 million International Units/m2	Three times weekly (For example, Monday, Wednesday and Friday)
Equal to or less than 0.5 m2	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).

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

Disease Overview

Chronic Granulomatous Disease

CGD is an inherited primary immunodeficiency caused by functional impairment of the dihydronicotinamide-adenine dinucleotide phosphate oxidase complex in neutrophilic granulocytes and monocytes characterized by recurrent and severe infections, dysregulated inflammation, and autoimmunity.[2] CGD may present any time from infancy to late adulthood; however, the vast majority of affected individuals are diagnosed before five years of age.[3] Some people with CGD do not have any identified genetic mutation. The cause of the condition in these individuals is unknown.[4] Mutations in the *CYBA, CYBB, NCF1, NCF2*, or *NCF4* gene can cause CGD.

The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology have jointly accepted responsibility for establishing the practice parameter for the diagnosis and management of primary immunodeficiency.[5] The practice parameter recommends patients with CGD be given prophylaxis with antimicrobial agents and Actimmune.

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 the bones brittle and susceptible to fracture. In some cases, this is also accompanied by skeletal abnormalities.[7] In about 30% 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*).[8] The Osteopetrosis Working Group developed expert consensus guidelines for the diagnosis and management of osteopetrosis.9 The guidelines recommend determination of diagnosis 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 suggest the use of Actimmune to be considered experimental in non-infantile osteopetrosis with limited clinical experience. Furthermore, the guidelines acknowledge the FDA indication for SMO and advise the indication pertains only to severe infantile osteopetrosis.

References

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