PRIOR AUTHORIZATION POLICY

POLICY: Interferon – Actimmune Prior Authorization Policy
- Actimmune® (interferon gamma-1b subcutaneous injection – Horizon)

REVIEW DATE: 05/14/2025

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. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

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) by which Actimmune has a 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.

Disease Overview

Chronic Granulomatous Disease (CGD)

CGD, a primary immune deficiency disease, is caused by defects in the nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase (NOX) enzyme.[2,3] This enzyme is needed by phagocytes (a type of white blood cell) to kill certain types of bacteria and fungi. Patients with CGD are at risk of contracting recurrent and sometimes severe bacterial or fungal

infections. Patients may need lifelong regimens of antibiotics and antifungals to prevent infections and use of Actimmune may also help reduce the number of severe infections. Mutations in one of five different genes that encode components of the NADPH (*CYBA, CYBB, NCF1, NCF2*, or *NCF4*) cause CGD. Some patients with CGD do not have an identified mutation in any of these genes and the cause of the condition in these individuals is unknown.

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.[4] The practice parameter (2015) recommends patients with CGD be given antibacterial and antifungal prophylaxis and Actimmune.

Severe, Malignant Osteopetrosis (SMO)
SMO is an inherited disorder characterized by osteoclast defect and deficient phagocyte oxidative metabolism.[1] There is a reduction in osteoclastic bone reabsorption, which results in bone density overgrowth and poor structural integrity (i.e., bones are more brittle and susceptible to fracture).[5,6] In some cases, this is also accompanied by skeletal abnormalities.[5] The cause of SMO is unknown in some patients, however, variants in one of the following genes have been found to be associated with osteopetrosis: *CA2, CLCN7, IKBLG, ITGB3, LRP5, OSTM1, PLEKHM1, SNX10, TCIRG1, TNFRSF11A, TNFSF11*. The Osteopetrosis Working Group developed expert consensus guidelines for the diagnosis and management of osteopetrosis (2017).[7] The guidelines recommend determination of diagnosis by classic radiographic (X-ray) features of osteopetrosis followed 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 that the indication pertains only to severe infantile osteopetrosis.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Actimmune. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actimmune as well as the monitoring required for adverse events and long-term efficacy, approval requires Actimmune to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

- **Actimmune® (interferon gamma-1b subcutaneous injection – Horizon)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Chronic Granulomatous Disease.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Diagnosis has been established by a molecular genetic test identifying a gene-related pathogenic variant linked to chronic granulomatous disease; AND
   Note: Examples of gene-related pathogenic variants linked to chronic granulomatous disease include biallelic pathogenic variants in *CYBA, CYBB, NCF1, NCF2*, and *NCF4*.

B) The medication is prescribed by or in consultation with an immunologist, a hematologist, or an infectious disease specialist.

2. **Malignant Osteopetrosis, Severe Infantile.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Diagnosis has been established by ONE of the following (i or ii):
      i. Patient has had radiographic (X-ray) imaging demonstrating skeletal features related to osteopetrosis; OR
      ii. Patient has had a molecular genetic test identifying a gene-related pathogenic variant linked to severe, infantile malignant osteopetrosis; AND
      Note: Examples of gene-related pathogenic variants linked to osteopetrosis include *CA2, CLCN7, IKBLG, ITGB3, LRP5, OSTM1, PLEKHM1, SNX10, TCIRG1, TNFRSF11A,* and *TNFSF11.*
   B) The medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT COVERED

- **Actimmune® (interferon gamma-1b subcutaneous injection – Horizon)**

is(are) considered not medically necessary for ANY other use(s).

REFERENCES

1. Actimmune® subcutaneous injection [prescribing information]. Lake Forest, IL: Horizon; December 2024.
2. National Institute of Allergy and Infectious Diseases. Chronic granulomatous disease (CGD). Available at: https://www.niaid.nih.gov/diseases-conditions/chronic-granulomatous-disease-cgd#:~:text=Chronic%20granulomatous%20disease%20(CGD)%20is,threatening%20bacterial%20and%20fungal%20infections. Last reviewed May 20, 2022. Accessed on May 7, 2025.
3. Genetics Home Reference. National Institutes of Health, U.S. National Library of Medicine. Available at https://ghr.nlm.nih.gov/. Accessed on May 7, 2025. Search terms: chronic granulomatous disease.
4. Bonilla F, Khan D, Ballas Z, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *The J Allergy Clin Immunol*. 2015;136(5):1186-1205.e78.
5. Charoenngam N, Nasr A, Shirvani A, Holick MF. Hereditary metabolic bone diseases: a review of pathogenesis, diagnosis and management. *Genes*. 2022;13:1880.
6. Genetics Home Reference. National Institutes of Health, U.S. National Library of Medicine. Available at https://ghr.nlm.nih.gov/. Accessed on May 7, 2025. Search terms: osteopetrosis.
7. Wu C, Econs M, DiMeglio L, et al. Diagnosis and management of osteopetrosis: consensus guidelines from the osteopetrosis working group. *J Clin Endocrinol Metab*. 2017;102:3111-3123.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Malignant Osteopetrosis, Severe Infantile:** Added Note for examples of genes linked to osteopetrosis.	04/05/2023
Annual Revision	No criteria changes.	05/29/2024

Selected Revision	**Chronic Granulomatous Disease:** The word "mutation(s)" was changed to "pathogenic variant." **Malignant Osteopetrosis, Severe Infantile:** In the criteria, the word "mutation" was changed to "pathogenic variant." Also, in the note, the word "genes" was clarified to state "gene-related pathogenic variants."	07/17/2024
Selected Revision	**Chronic Granulomatous Disease:** Regarding the specialist requirement, a hematologist or an infectious disease specialist were added; previously only an immunologist was listed.	09/18/2024
Annual revision	No criteria changes.	05/14/2025