PreferredOne® ATION POLICY

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

DATE REVIEWED: 04/15/2020

OVERVIEW

Actimmune is indicated for reducing the frequency and severity of serious infections associated with chronic granulomatous disease (CGD) of patients ≥ 1 year of age.[1] Actimmune is also indicated for delaying time to disease progression age with severe, malignant osteopetrosis (SMO) of patients ≥ 1 month of age. Actimmune has shown a treatment-related enhancement of superoxide production by phagocytes and was found to enhance osteoclast function in vivo. Actimmune, an interferon gamma, is a single-chain polypeptide containing 140 amino acids. Specific effects of interferon gamma include the enhancement of the oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity, activation of natural killer cells, and the expression of Fc receptors and major histocompatibility antigens.[1]

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.[2] CGD may present any time from infancy to late adulthood; however, the vast majority of affected individuals are diagnosed before age five years.[3] Some people with chronic granulomatous disease do not have any identified mutation gene. 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 & 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.[5] 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.[6] 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 153 of 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 them brittle and susceptible to fracture. In some cases, this is also accompanied by skeletal abnormalities.[7] 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).[8] The Osteopetrosis Working Group developed expert consensus guidelines for the diagnosis and management of osteopetrosis.[9] 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.

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.[1]

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actimmune is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Chronic Granulomatous Disease.** Approve for 1 year if the patient meets of the following criteria (A and B):
   - **A)** Diagnosis has been established by a molecular genetic test identifying a gene-related mutation linked to chronic granulomatous disease; AND
     Note: Examples of gene-related mutations 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.

2. **Malignant Osteopetrosis, Severe Infantile.** Approve for 1 year if the patient meets of the following criteria (A and B):
   - **A)** Diagnosis has been established by one of the following (i or ii)
     - **i.** Patient has had a radiographic (X-ray) imaging demonstrating skeletal features related to osteopetrosis; OR
     - **ii.** Patient has had a molecular genetic test identifying a gene-related mutation linked to malignant osteopetrosis, severe infantile; AND
   - **B)** The medication is prescribed by, or in consultation with, an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Actimmune has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Actimmune® subcutaneous injection [prescribing information]. Lake Forest, IL: Horizon Pharma USA; December 2019.
2. Arnold D, Heimall J. A review of chronic granulomatous disease. *Advanced Therapy.* 2017;34:2543-2557.
3. Genetic Testing Registry. National Center for Biotechnology Information. Available at https://www.ncbi.nlm.nih.gov/gtr/conditions/C1856245/. Accessed on March 30, 2020.
4. Genetics Home Reference. National Institutes of Health, U.S. National Library of Medicine. Available at https://ghr.nlm.nih.gov/. Accessed on March 30, 2020. Search terms: chronic granulomatous disease
5. Bonilla F, Khan D, Ballas Z, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *The Journal of Allergy and Clinical Immunology*. 2015;136:5:1186-1205.e78.
6. Yu J, Azar A, Chong H, et al. Considerations in the diagnosis of chronic granulomatous disease. *Journal of the Pediatric Infectious Disease Society.* 2018;7:S6-S11.
7. Stark Z, Savarirayan R. Osteopetrosis. *Orphanet Journal of Rare Diseases.* 2009;4:5.
8. Genetics Home Reference. National Institutes of Health, U.S. National Library of Medicine. Available at https://ghr.nlm.nih.gov/. Accessed on March 30, 2020. Search terms: osteopetrosis
9. Wu C, Econs M, DiMeglio L, et al. Diagnosis and management of osteopetrosis: consensus guidelines from the osteopetrosis working group. *The Journal of Clinical Endocrinology & Metabolism*. 2017;102:9:3111-3123.

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PreferredOne Community Health Plan
PO Box 59052
Minneapolis, MN 55459-0052
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Fax: 763.847.4010
customerservice@preferredone.com

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U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

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U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

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