Clinical Policy: Interferon Gamma-1b (Actimmune)

Reference Number: PA.CP.PHAR.52
Effective Date: 01/18
Last Review Date: 01/19

Coding Implications
Revision Log

Description
Interferon gamma-1b (Actimmune®) is a recombinant form of gamma interferon.
FDA Approved Indication(s)
Actimmune is indicated for:

- Reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD)
- Delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO)

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness® that Actimmune is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Granulomatous Disease (must meet all):
1. Age ≥ 1 year;
2. Diagnosis of chronic granulomatous disease (CGD);
3. Prescribed by or in consultation with a hematologist or infectious disease specialist;
4. Prescribed dose does not exceed one of the following (a or b):
   a. Body surface area > $0.5m^2$: 50 mcg/m^2 three times weekly;
   b. Body surface area ≤ $0.5m^2$: 1.5mcg/kg three times weekly.

Approval duration: 6 months

B. Severe Malignant Osteopetrosis (must meet all):
1. Age ≥ 1 month;
2. Diagnosis of severe malignant osteopetrosis (SMO) (also known as autosomal recessive osteopetrosis) confirmed by radiographic imaging;
3. Prescribed by or in consultation with an endocrinologist;
4. Prescribed dose does not exceed one of the following (a or b):
   a. Body surface area > $0.5m^2$: 50mcg/m^2 three times weekly;
   b. Body surface area ≤ $0.5m^2$: 1.5mcg/kg three times weekly.

Approval duration: 6 months

C. Mycosis Fungoides, Sezary Syndrome (off-label) (must meet all):
1. Diagnosis of mycosis fungoides or Sezary syndrome;
2. Age ≥ 1 month;
3. Prescribed by or in consultation with an oncologist;
4. Request meets one of the following (a, b, or c):
   a. BSA > 0.5 m^2: Dose does not exceed 50 mcg/m^2 three times weekly;
   b. BSA ≤ 0.5 m^2: Dose does not exceed 1.5 mcg/kg three times weekly;

c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Other diagnoses/indications: Refer to CP.PMN.53
Approval duration: 6 months

II. Continued Approval

A. All Indications in Section I (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, requestmeets one of the following (a, b, or c):
   a. BSA > 0.5 m^2: New dose does not exceed 50 mcg/m^2 three times weekly;
   b. BSA ≤ 0.5 m^2: New dose does not exceed 1.5 mcg/kg three times weekly.
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Other diagnoses/indications (1 or 2):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or Continuity of Care Policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

III. Appedices/General Information

Appendix A: Abbreviation/Acronym Key

BSA: body surface area
CGD: chronic granulomatous disease
FDA: Food and Drug Administration
SMO: severe, malignant osteopetrosis

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity
- Boxed warning(s): none reported

Appendix D: General Information

- The manufacturer's pivotal study for Actimmune showed the drug offered no benefit versus placebo for primary study endpoints for idiopathic pulmonary fibrosis. Analysis of secondary endpoints demonstrated a trend toward increased overall survival in patients

treated with Actimmune with baseline forced vital capacity (FVC) > 70% of predicted. An analysis reported that patients with FVC > 55% also benefited. However, the subgroup with FVC > 60% of predicted did not. Therefore, use of baseline FVC to predict benefit is at best speculative at this time.

- A second post-hoc analysis also indicated no benefit in mortality if a dose of > 100 mcg/m^2 was administered. Additional clarification of appropriate dosing needs to occur. Detailed data on cause of death was not provided. It is currently impossible to speculate that Actimmune was the cause of reduced overall mortality. The absolute number of deaths differed by eight in the study.
- NCCN Compendium lists Actummune with a category 2A recommendation for the treatment of mycosis fungoides and Sezary syndrome as primary therapy, treatment for refractory or progressive disease, or in combination with phototherapy, retinoids, or photopheresis.
- Positive response in CGD may include reduction in frequency and severity of serious infections associated with CGD or no disease progression while on therapy.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CGD, SMO	BSA > 0.5 m^2: 50 mcg/m^2 SC TIW BSA $\leq$ 0.5 m^2: 1.5 mcg/kg/dose SC TIW	See dosing regimen

V. Product Availability

Single-use vial for injection: 100 mcg (2 million IU)/0.5 ml

Background

Description/Mechanism of Action:

Actimmune (interferon gamma-1b), an interferon gamma, is a single-chain polypeptide containing 140 amino acids. Production of Actimmune is achieved by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the recombinant protein. Interferons bind to specific cell surface receptors and initiate a sequence of intracellular events that lead to the transcription of interferon-stimulated genes. The three major groups of interferons (alpha, beta, and gamma) have partially overlapping biological activities that include immunoregulation such as increased resistance to microbial pathogens and inhibition of cell proliferation. Type 1 interferons (alpha and beta) bind to the alpha/ beta receptor. Interferon gamma binds to a different cell surface receptor and is classified as Type 2 interferon. 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.

- CGD is an inherited disorder of leukocyte function caused by defects in the enzyme complex responsible for phagocyte superoxide generation. Actimmune does not increase phagocyte superoxide production even in treatment responders.
- In SMO (an inherited disorder characterized by an osteoclast defect, leading to bone overgrowth, and by deficient phagocyte oxidative metabolism), a treatment-related

enhancement of superoxide production by phagocytes was observed. Actimmune was found to enhance osteoclast function in vivo.

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.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9216	Injection, interferon, gamma 1-b, 3 million units

Reviews, Revisions, and Approvals	Date	Approval Date
Removed diagnostic confirmatory tests and replaced with specialty prescriber requirement. References reviewed and updated.	02/18	
1Q 2019 annual review: references reviewed and updated.	01/19	

References
1. Actimmune Prescribing Information. Lake Forest, IL: Horizon Pharma USA, Inc., May 2017. Available at: www.actimmune.com. Accessed October 25, 2018.
2. Stark Z, Savarirayan R. Osteopetrosis. *Orphanet J Rare Dis.* 2009; 4(5): 1-12.
3. Wilson CJ, Vellodi A. Autosomal recessive osteopetrosis: diagnosis, management, and outcome. *Arch Dis Child.* 2000; 83(5): 449-452.
4. Key LL Jr, Rodriguiz RM, Willi SM, et al. Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med.* 1995; 332(24): 1594-1599.
5. Interferon Gamma-1b. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed October 25, 2018.