Interferon gamma-1b (Actimmune®)

Policy # 00212
Original Effective Date: 10/18/2006
Current Effective Date: 01/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider interferon gamma-1b (Actimmune®)‡ to reduce the frequency and severity of infections associated with chronic granulomatous disease (CGD) to be **eligible for coverage.****

Based on review of available data, the Company may consider interferon gamma-1b (Actimmune) to delay the progression of severe, malignant osteopetrosis to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of interferon gamma-1b (Actimmune) for non- Food and Drug Administration (FDA) approved indications to be **investigational.***

Background/Overview

Interferon gamma-1b is a bioengineered form of interferon gamma, a protein that acts as a biologic response modifier to stimulate the human immune system. It is a sterile, clear, colorless solution filled in a single-dose vial for subcutaneous injection. This medication has been proven safe and effective in children and adults with chronic granulomatous disease (CGD) and osteopetrosis.

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Chronic granulomatous disease is an inherited abnormality of the immune system that normally kills phagocytic cells. The inability of phagocytic cells to kill certain bacteria and fungi leads to long term and repeated infections. The condition is often discovered in the first years of life. Milder forms may appear in adolescence or even adulthood. Impetigo, skin abscess and furuncles, and perianal and rectal abscess, recurrent pneumonia and chronic swelling of the lymph nodes in the neck with abscess formation are common. The incidence of CGD is about one in a million.

Osteopetrosis is a congenital condition present at birth in which the bones are overly dense. With osteopetrosis, the cells that break down bone, or the osteoclasts, usually are either fewer in numbers or are ineffective in breaking down bone. This condition affects all the bones of the body. The bones are overly dense, and the skeleton is extremely heavy. The increased bone mass reduces the space available for bone marrow and narrows the passages through which nerves pass in the skull. In severe forms of osteopetrosis the reduced bone marrow cavity cannot support adequate development of blood cells, which causes thrombocytopenia, anemia and infections.

Malignant Osteopetrosis is the most severe type of osteopetrosis and is inherited when both parents have an abnormal gene that is passed to the child. The disease is apparent from birth and ends in death. This disease is not related to cancer. Children with this condition have:

- Anemia (and frequently complete marrow failure)
- Frequent infections due to a reduction in white blood cells (the cells that fight infection) and to inactive white cells.
- No tooth eruption or inadequate tooth eruption from the gums.
- Increased pressure within the skull.
- Failure to thrive.
- Delays in psychomotor development, including delays in sitting, walking and talking.
- Blindness, deafness and other nerve problems within the head.
- Death during the first ten years of life in 30 percent of these children.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 1990, the FDA approved Actimmune for reducing the frequency and severity of serious infections associated with chronic granulomatous disease (CGD), a rare, inherited deficiency of the immune

system that leaves patients vulnerable to frequent and severe bacterial and fungal infections. These infections often require hospitalization and can be fatal.

In February 2000, the FDA approved Actimmune for delaying the time to disease progression in patients with severe, malignant osteopetrosis.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Chronic Granulomatous Disease (CGD)

A randomized, double-blind, placebo-controlled study was performed to determine whether Actimmune administered subcutaneously on a three times weekly schedule could decrease the incidence of serious infectious episodes and improve existing infectious and inflammatory conditions in patients with chronic granulomatous disease (CGD). One hundred twenty-eight eligible patients were enrolled on this study including patients with different patterns of inheritance. Most patients received prophylactic antibiotics. Patients ranged in age from 1 to 44 years with the mean age being 14.6 years. The study was terminated early following demonstration of a highly statistically significant benefit of Actimmune therapy compared to placebo with respect to time to serious infection ($p = 0.0036$), the primary endpoint of the investigation. Serious infection was defined as a clinical event requiring hospitalization and the use of parenteral antibiotics. The final analysis provided further support for the primary endpoint ($p = 0.0006$). There was a 67 percent reduction in relative risk of serious infection in patients receiving Actimmune ($n = 63$) compared to placebo ($n = 65$). Additional supportive evidence of treatment benefit included a twofold reduction in the number of primary serious infections in the Actimmune group (30 on placebo versus 14 on Actimmune $p = 0.002$) and the total number and rate of serious infections including recurrent events (56 on placebo versus 20 on Actimmune $p = 0.0001$). Moreover, the length of hospitalization for the treatment of all clinical events provided evidence highly supportive of an Actimmune treatment benefit. Placebo patients required 3 times as many inpatient hospitalization days for treatment of clinical events compared to patients receiving Actimmune (1,493 versus 497 total days, $p = 0.02$).

An Actimmune treatment benefit with respect to time to serious infection was consistently demonstrated in all subgroup analyses according to stratification factors, including pattern of inheritance, use of prophylactic antibiotics, as well as age. There was a 67 percent reduction in relative risk of serious infection in patients receiving Actimmune compared to placebo across all groups. The beneficial effect of Actimmune therapy was observed throughout the entire study, in which the mean duration of Actimmune administration was 8.9 months/patient.

Severe, Malignant Osteopetrosis
A controlled, randomized study in patients with severe, malignant osteopetrosis was conducted with Actimmune administered subcutaneously three times weekly. Sixteen patients were randomized to receive either Actimmune plus calcitriol (n = 11), or calcitriol alone (n = 5). Patients ranged in age from 1 month to 8 years, mean 1.5 years. Treatment failure was considered to be disease progression as defined by 1) death, 2) significant reduction in hemoglobin or platelet counts, 3) a serious bacterial infection requiring antibiotics or 4) a 50 dB decrease in hearing or progressive optic atrophy. The median time to disease progression was significantly delayed in the Actimmune plus calcitriol arm versus calcitriol alone. In the treatment arm, the median was not reached. Based on the observed data, however, the median time to progression in this arm was at least 165 days versus a median of 65 days in the calcitriol alone arm. In an analysis which combined data from a second study, 19 of 24 patients treated with Actimmune plus or minus calcitriol for at least 6 months had reduced trabecular bone volume compared to baseline.

References

1. American Society of Health–Systems Pharmacists. Interferon Gamma. www.ahfsdrugintormation2007.com.
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4. Medline Plus, Medical Encyclopedia: Chronic Granulomatous Disease. www.medlineplus.gov May 30, 2006.
5. National Institutes of Health Osteoporosis and Related Bone Disease, National Resource Center. Information for Patients with Osteopetrosis-Fact Sheet. www.osteo.org, Published date: 08/2000.
6. Actimmune [package insert]. Horizon Therapeutics. Dublin, Ireland. Updated March 2021.

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10/04/2006	Medical Director review
10/18/2006	Medical Policy Committee approval
10/10/2007	Medical Director review
10/17/2007	Medical Policy Committee approval, no change to policy statement
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee approval
10/14/2009	Medical Policy Implementation Committee approval. Off-label is considered non-covered.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. Updated background and rationale/source sections. No coverage changes.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. No change to coverage.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J9216
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.