Immune Globulin Therapy (Asceniv™, Bivigam®, Cutaquig®)

Medicare Advantage Medical Policy No.: MNG-016

The Health Plan reserves the right to amend this policy and procedure at any time. Exceptions to this policy and procedure will be made on a case-by-case basis at the total discretion of the Health Plan.

Effective Date: May 28, 2024

Medicare Advantage Members

Coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria will be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of the coverage criteria and is to be used by all plans and lines of business unless Federal or State law, contract language, including member or provider contracts, take precedence over the policy.

Basic Requirements for Clinical Appropriateness:

1. Before diagnostic or therapeutic intervention, a clinician must confirm the diagnosis or establish the likelihood based on a history and physical exam and, when appropriate, a review of laboratory studies, previous diagnostic testing and response to any prior interventions, specifically relevant to the clinical situation.
2. An alternative treatment or other appropriate intervention should not offer any greater benefit based on standards of medical practice and/or current literature.
3. The potential benefit to the patient should outweigh the risk of the diagnostic or therapeutic intervention.
4. A reasonable likelihood of the intervention changing management and/or leading to an improved outcome for the patient must exist, based on the clinical evaluation, current literature and standards of medical practice.

If these requirements are not apparent in the request for authorization, including the clinical documentation provided, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous ordering of multiple diagnostic or therapeutic interventions and/or repeated diagnostic or therapeutic interventions in the same anatomic area may be denied, unless individual circumstances

support the medical necessity of performing interventions simultaneously or repeatedly. This should be apparent in the clinical documentation or in peer-to-peer conversations.

Immune Globulin Therapy (Asceniv™, Bivigam®, Cutaquig®)

When Services May Be 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.*

Immune globulin therapy with Asceniv™ and Bivigam® (both intravenous immune globulin-IVIG) and Cutaquig® (subcutaneous immune globulin-SCIG) are covered for all FDA approved indications. All immune globulins referenced above are covered at parity status.

Intravenous Immune Globulin (IVIG)

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG). Low dose therapy can replace missing antibodies and protect against a wide range of infections for people with health conditions that lower antibody levels, such as immune deficiencies.

Based on review of available data, the Health Plan considers intravenous immune globulin (IVIG) therapy with Asceniv™ or Bivigam® to be eligible for coverage as follows:

Asceniv™ (immune globulin intravenous, human – slra, 10% liquid)

Asceniv is used for, but not limited to, the following indications in adults and adolescents (12 to 17 years of age):

Primary Humoral Immunodeficiency (PI)

- Congenital agammaglobulinemia;
- Common variable immunodeficiency (CVID);
- X-linked agammaglobulinemia (Bruton's);
- Wiskott-Aldrich syndrome (WAS);
- Severe combined immunodeficiencies;
- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immune globulin:
    - Laboratory evidence of immunoglobulin deficiency;
    - Documented inability to mount an adequate immunologic response to inciting antigens;
    - Persistent, severe infections despite treatment with prophylactic antibiotics.

Bivagam® (immune globulin g intravenous, human, 10% injection, solution)

Bivigam is used for, but not limited to, the following indications in adults and pediatric patients 2 years of age and older:

Primary Humoral Immunodeficiency (PI)

- Common variable immunodeficiency (CVID)
- X-linked agammaglobulinemia®
- Congenital agammaglobulinemia
- Wiskott-Aldrich syndrome
- Severe combined immunodeficiencies (SCID)
- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immune globulin:
    - Laboratory evidence of immunoglobulin deficiency;
    - Documented inability to mount an adequate immunologic response to inciting antigens;
    - Persistent, severe infections despite treatment with prophylactic antibiotics.

Subcutaneous Immune Globulin (SCIG) Therapy

Subcutaneous immune globulin (SCIG) is a blood product made from plasma collected from human blood donors. SCIG contains special proteins (antibodies) which helps to fight infections. It is injected under the skin (subcutaneously).

Based on review of available data, the Health Plan considers subcutaneous immune globulin (SCIG) therapy with Cutaquig® to be eligible for coverage as follows:

Cutaquig® (immune globulin subcutaneous, (human) – hipp), 16.5% solution)

Cutaquig is used for, but not limited to, the following indications in adults and pediatric patients 2 years of age and older:

Primary Humoral Immunodeficiency (PI)

- Common variable immunodeficiency (CVID)
- X-linked agammaglobulinemia
- Congenital agammagloblinemia
- Wiskott-Aldrich syndrome
- Severe combined immunodeficiencies (SCID)
- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immune globulin:
    - Laboratory evidence of immunoglobulin deficiency;
    - Documented inability to mount an adequate immunologic response to inciting antigens;
    - Persistent, severe infections despite treatment with prophylactic antibiotics.

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 Health Plan considers the use of Asceniv™, Bivigam® and Cutaquig® for non-FDA approved indications to be investigational.* Off label use may be considered with appropriate clinical documentation.

Background/Overview

Human immune globulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Delivery of IVIG and SCIG are typically used for conditions treated in an outpatient setting.

Intravenous infusion immune globulin is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contain antibodies to greater than 10 million antigens. Intravenous immune globulin therapy has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis.

Subcutaneous infusion immune globulin is used for treating patients with PID. A genetic basis for more than 80 different types of PID has been discovered, with the most common type being primary antibody deficiency (PAD) that is associated with low levels or total lack of normal circulating immunoglobulins.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Both Asceniv™ (ADMA Biologics) and Bivigam® (ADMA Biologics) have been approved by the FDA as IVIG therapy for PI.

Cutaquig® (Octapharma) has been approved by the FDA as SCIG therapy for PI.

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.

Primary Immune Deficiency (PI)

Primary humoral immunodeficiency deficiencies refer to diseases resulting from impaired antibody production because of a molecular defect intrinsic to B cells or a failure of interactions between B and T cells. Antibody deficiency characteristically leads to recurrent, often severe upper and lower respiratory tract infections. Findings associated with severe primary humoral immunodeficiencies include failure to thrive, chronic diarrhea, recurrent fever, nodular lymphoid hyperplasia in the gut, and hepatosplenomegaly.

Asceniv™ was granted approval by the FDA in 2019 for the treatment of PI in adults and adolescents 12 to 17 years of age. Approval was based on results from a phase III prospective, open-label,

nonrandomized, multicenter clinical study that evaluated 59 patients with PI at 9 sites across the United States. For the study, regular infusions of Asceniv™ were given to the patients over the course of 1 year. According to the study, there were no serious bacterial infections (SBIs) in the treated patients during the 12-month study period. Serious bacterial infections are defined as bacteremia/sepsis, bacterial meninigitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess.

The most common adverse effects reported during the study were headache, sinusitis, nasopharyngitis, upper respiratory tract infection, bronchitis, viral gastroenteritis, diarrhea, and nausea. The approved labeling includes a boxed warning about potential thrombosis and renal disfunction or failure.

According to ADMA Biologics, Inc., Asceniv™ is manufactured using its unique, patented plasma donor screening methodology and tailored plasma pooling design, blending normal source plasma and plasma from donors tested using its proprietary microneutralization assay.

Bivigam®, initially manufactured by Biotest Pharmaceuticals Corporation, received FDA approval for the treatment of patients 12 years of age and older with PI in December 2012. Approval was based on a phase IV prospective, open-label, single-arm, multi-center clinical trial evaluating the safety, efficacy, and pharmacokinetics of Bivigam® in pediatric patients with a documented diagnosis of PI, including hypogammaglobulinemia or agammaglobulinemia. The study was conducted in six centers in the United States and included 18 male and female patients aged 2 to 16 years who received Bivigam® infusions every 3 or 4 weeks for approximately 5 months. According to the study, the primary efficacy endpoint was the incidence of acute SBIs during the 5-month study observation period. There were no acute SBIs that occurred during the observation period. For the secondary efficacy results, there were 17 non-serious infections but none that required hospitalizations or IV antibiotics during the study.

ADMA Biologics, Inc. (ADMA) acquired the Biotest Therapy Business Unit assets in June 2017, of which Bivigam® was a part, and resumed the production of Bivigam®. Using ADMA's optimized IVIG manufacturing process, the FDA approved ADMA's Prior Approval Supplement and enabled ADMA to commence the marketing and commercial sale of Bivigam® in 2019.

In December 2023, Bivagam® received FDA expanded approval for treating PI in patients 2 years of age and older. The approval was based on data obtained from a second Phase IV, multi-center, open-label study which was part of the Bivigam® post marketing requirement. It was conducted in 4 centers across the U.S. on 16 male and female patients with PI, aged 2 to 16. Inclusion criteria required that the patients had received IVIG therapy which was maintained at a steady dose for at least 3 months prior to study entry and had maintained a trough IgG level at least 500 mg/dl prior to receiving Bivigam®. Results were submitted to ClinicalTrials.gov in February 2024, but are not yet publicly posted.

Cutaquig®, manufactured by Octapharma and distributed by Pfizer Labs, received initial FDA approval in 2018 as replacement therapy for PI in adults. In December 2021, the FDA approved Cutaquig® for the treatment of pediatric patients aged 2 years and older with PI. Approval was based on the results of data obtained from 2 clinical trials, with one being a pivotal, prospective, open-label, single-arm, multicenter, multinational Phase III pivotal study. Trial sites were held in North America and Europe. The other was an extension study.

The pivotal study included 75 patients with PI (37 adults, with the oldest being 73 years old, and 38 pediatric patients, aged 2 through 17 years) who received weekly subcutaneous infusions with

Cutaquig® during a 12-week wash-in/wash-out period followed by a 12-month efficacy period during which efficacy, pharmacokinetics, safety, tolerability, and quality of life parameters of Cutaquig® were evaluated. Overall, 36 female patients and 39 male patients participated in the study. The mean age in the adult group (17-75) was 47.5 years. The mean age at time of enrollment in the pediatric groups was 4.2 years, 7.9 years, and 14.1 years in the 3 pediatric age groups (ages 2-5 years, 6-11 years, and 12-16 years respectively). Reported race was white for all but one patient, and all were not of Hispanic/Latino ethnicity. Sixty-eight patients completed the study. Seven patients (4 adolescents and 3 adults) were withdrawn prematurely. Reasons for withdrawal from the study were patient's decision in 6 cases and patient's non-compliance in one adolescent patient. As the main objective of the study was to assess the efficacy of Cutaquig®, criterion was met, as no SBIs were reported.

The extension study was a prospective, open-label, single-arm, multicenter Phase III study that included 27 patients, (17 adult patients and 10 pediatric patients, aged <17 years) with PI. Twenty-one patients were rolled over from the pivotal study and 6 patients were newly enrolled. Mean age was 39 years, ranging from 6 to 73 years. Ten patients (37%) were male, all but 2 were White, and none were Hispanic or Latino. Twenty-five patients received weekly subcutaneous infusions with Cutaquig® while 2 were on an "every other week" schedule. The primary objective of this study was to assess the medium-to-long term safety and tolerability of Cutaquig®. Secondary efficacy assessments included occurrence of SBIs, the annual rate of any kind or seriousness, hospitalizations due to infections, and antibiotic use. One adult had bacteremia/sepsis. The rate of SBI per person-year was 0.03 for adults, and 0.0 for all other age groups (overall rate of 0.018). The most common adverse reactions in > 5% of study subjects were local infusion site adverse reactions, (e.g., redness, swelling, and itching), headache, fever, dermatitis, asthma, diarrhea, and cough.

Thrombosis may occur with immune globulin products, and risk factors may include advanced age, cardiovascular risks, estrogen use, history of arterial or venous thrombosis, hypercoagulable conditions, hyperviscosity, prolonged immobilization, and indwelling vascular catheters.

The similar clinical efficacy of SCIG replacement therapy versus IVIG, in the context of a simpler delivery method for chronic therapy and some evidence of improved quality of life, suggests SCIG treatment may be considered medically necessary in lieu of IVIG to prevent recurrent infections in patients with primary immunodeficiency who require lifelong immunoglobulin replacement therapy.

References:

1. Asceniv™ [package insert]. ADMA Biologics, Inc. Boca Raton, FL. Updated March 15, 2024.
2. Bivigam® [package insert]. ADMA Biologics, Inc. Boca Raton, FL. Updated May 7, 2024.
3. Cutaquig® [package insert]. Octapharma Pharmazeutika Produktionsges m.b.H. Vienna, AUT. Revised Nov 2021.
4. Food and Drug Administration (FDA). Vaccines, Blood & Biologics: Immune Globulins. 2023; www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Accessed May 15, 2024.

Policy History

Original Effective Date: 05/28/2024

05/28/2024: UM Committee review and approval.

Coding

The five-character codes included in this medical policy are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 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:

CPT Code	Description
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
HCPCS Code	Description
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1554	Injection, immune globulin (Asceniv™), 500 mg
J1556	Injection, immune globulin (Bivigam®), 500 mg.
ICD-10 Dianosis	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. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    2. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Healthcare 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 healthcare 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 Health Plan 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 Health Plan 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.