Provider Administered Drugs – Site of Care

Guideline Number: MMG141.AF
Effective Date: April 1, 2024

➲ Instructions for Use

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Related Medical Management Guidelines

- Home Health, Skilled, and Custodial Care Services
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Coverage Rationale

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This guideline addresses the criteria for consideration of allowing hospital outpatient facility infusion services for specialty medications and intravenous Immune Globulin (IVIG) and subcutaneous Immune Globulin (SCIG) therapy. This includes claim submission for hospital-based services with the following CMS/AMA Place of Service codes:

- 19 Off Campus-Outpatient Hospital; and
- 22 On Campus-Outpatient Hospital

Alternative Sites of Care, such as non-hospital outpatient infusion, physician office, ambulatory infusion suites, or home infusion services are well accepted places of service for medication infusion therapy. If an individual does not meet criteria for outpatient hospital facility infusion, alternative sites of care may be used.

Outpatient hospital facility-based intravenous medication infusion is medically necessary for individuals who meet at least one of the following criteria (submission of medical records is required):

- Documentation that the individual is medically unstable for administration of the prescribed medication at the alternative sites of care as determined by any of the following:
  - The individual's complex medical status or therapy requires enhanced monitoring and potential intervention above and beyond the capabilities of the alternate Site of Care; or
  - The individual's documented history of a significant comorbidity (e.g., cardiopulmonary disorder or fluid overload) status that precludes treatment at an alternative Site of Care; or
  - Treatment at an alternate Site of Care setting presents a health risk due to a clinically significant physical or cognitive impairment; or
  - Difficulty establishing and maintaining patent vascular access

  or
- Documentation (e.g., infusion records, medical records) of episodes of severe or potentially life-threatening adverse events (e.g., anaphylaxis, seizure, thromboembolism, myocardial infarction, renal failure), not including the first or second infusion and, while receiving requested therapy that have not been responsive to acetaminophen, steroids, diphenhydramine, fluids,

infusion rate reductions, or other pre-medications, thereby increasing risk to the individual when administration at an alternate Site of Care; or
- Initial infusion or re-initiation of therapy after more than 6 months for a short duration of time (e.g., 4 weeks); or
- For IVIG or SCIG only: Individual has immunoglobulin A (IgA) deficiency with anti-IgA antibodies; or
- Homecare or infusion provider has deemed that the individual, home caregiver, or home environment is not suitable for home infusion therapy and both of the following:
  - The prescriber is unable to infuse in the office setting
  - There are no ambulatory infusion suite options available for this member

Ongoing outpatient hospital facility-based infusion duration of therapy will be no more than 6 months to allow for reassessment of the individual's ability to receive therapy at an alternative Site of Care.

Note: If more than one of the above criteria are met, then the greatest of the applicable approval time periods will be allowed.

This guideline applies to these medications that require healthcare provider administration:

- Asceniv™ (IV)
- Bivigam® (IV)
- Carimune® NF (IV)
- Cutaquig® (SC)
- Cuvitru® (SC)
- Flebogamma® DIF (IV)
- Gammagard® Liquid (IV, SC)
- Gammagard® S/D (IV)
- Gammaked™ (IV, SC)
- Gammaplex® (IV)
- Gamunex®-C (IV, SC)
- Hizentra® (SC)
- HyQvia® (SC)
- Octagam® (IV)
- Panzyga® (IV)
- Privigen® (IV)
- Soliris® (eculizumab)
- Xembify® (SC)

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Specialty Medications		Required Clinical Information
Asceniv™ (IV)	Gammaplex® (IV)	Refer to the applicable Medical Benefit Drug Policy.
Bivigam® (IV)	Gamunex®-C (IV, SC)	
Carimune® NF (IV)	Hizentra® (SC)	
Cutaquig® (SC)	HyQvia® (SC)	
Cuvitru® (SC)	Octagam® (IV)	
Flebogamma® DIF (IV)	Panzyga® (IV)	
Gammagard® Liquid (IV, SC)	Privigen® (IV)	
Gammagard® S/D (IV)	Soliris® (Eculizumab)	
Gammaked™ (IV, SC)	Xembify® (SC)	

Definitions

The following definitions may not apply to all plans. Refer to the member specific benefit plan document for applicable definitions.

Immune Globulin: Immune Globulins are components of the immune system. There are several types of Immune Globulin produced by the body (e.g., IgA, IgD, IgE, IgG, IgM). This medical policy addresses therapeutic use of Immune Globulin G (IgG) an antibody normally produced by B lymphocytes. References to Immune Globulin within this medical policy refer to IgG. IgG products have been referred to in multiple ways, some of which are: Immune Globulin (IG), immunoglobulin, gamma globulin, and by its route of administration - intravenous Immune Globulin (IVIG), Immune Globulin intravenous (IGIV), subcutaneous Immune Globulin (SCIG), Immune Globulin subcutaneous (IGSC).

Site of Care: Choice for physical location of infusion administration. Sites of Care include hospital inpatient, hospital outpatient, physician office, ambulatory infusion suite, or home-based setting.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each

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HCPCS Code	Description
J1300	Injection, eculizumab, 10 mg
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1554	Injection, immune globulin (Asceniv), 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (Xembify), 100 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, 100 mg immune globulin
J1576	Injection, immune globulin (Panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg

Description of Services

According to the American Academy of Allergy Asthma and Immunology (AAAI), Immunoglobulin G (IgG) is a type of antibody in blood plasma. Individuals who suffer from immunodeficiency diseases involving low IgG levels and/or function may, under certain circumstances, benefit from immunoglobulin replacement therapy, also known as IVIg or SCIg. The IgG can be administered each month intravenously or under the skin (subcutaneous, SCIg) once a week or bi-weekly. Both methods are effective at replacing IgG with levels essential to fight infections. Each technique has pros and cons that should be discussed with an allergist/immunologist. IgG replacement therapy is commonly well tolerated, though side effects such as allergic reactions and headaches can occur. (AAAAI., 2022)

As hospital settings can relate to a risk of introducing individuals with infectious conditions, the benefits of outpatient and home therapy should serve as an incentive to reexamine an individual and their appropriateness for a specific Site of Care. (AAAI., 2011)

Benefit Considerations

This guideline applies to members with benefits available for health care services if medically necessary and have been approved for the requested medication clinical use.

Clinical Evidence

Home infusion as a place of service is well established and accepted by physicians. A 2010 home infusion provider survey by the National Home Infusion Association reported providing 1.24 million therapies to approximately 829,000 patients, including 129,071 infusion therapies of specialty medications.

In a trial evaluating patients with paroxysmal nocturnal hemoglobinuria, after initial 2-5 doses of eculizumab (Soliris), 79 patients received continued infusion with every 14 days in the home setting for the duration of the study – 1-98 months, mean duration of 39 months. The survival of patients treated with eculizumab was not different from age- and sex-matched normal controls (P = .46) but was significantly better than 30 similar patients managed before eculizumab (P = .030). Three patients on eculizumab, all over 50 years old, died of causes unrelated to PNH. Twenty-one patients (27%) had a thrombosis before starting eculizumab (5.6 events per 100 patient-years) compared with 2 thromboses on eculizumab (0.8 events per 100 patient-years; P < .001). Twenty-one patients with no previous thrombosis discontinued warfarin on eculizumab with no thrombotic sequelae. Forty of 61 (66%) patients on eculizumab for more than 12 months achieved transfusion independence. The 12-month mean transfusion requirement reduced from 19.3 units before eculizumab to 5.0 units in the most recent 12 months on eculizumab (P < .001). Eculizumab dramatically alters the natural course of PNH, reducing symptoms and disease complications as well as improving survival to a similar level to that of the general population.

Infliximab has been shown to be safely infused in the community setting. A chart review of 3161 patients who received a combined 20,976 infusions in community clinics was conducted to evaluate safety across all types of patients. Infliximab infusions are safe in the community setting. Severe ADRs were rare. A total of 524 (2.5% of all infusions) acute ADRs in 353 patients (11.2%) were recorded. Most reactions (i.e., ADRs) were mild (N = 263 [50.2%, 1.3% of all infusions]) or moderate (N = 233 [44.5%, 1.1% of all infusions]). Twenty-eight reactions (5.3%, 0.1% of all infusions) were severe. Emergency medical services were called to transport patients to hospital for seven of the severe reactions, of which none required admission. As per pre-established medical directives adrenaline was administered three times. The authors concluded that infliximab infusions are safe in the community setting. Severe ADRs were rare. None required active physician intervention; nurses were able to treat all reactions by following standardized medical directives. Ten children were enrolled in the home infusion program if they were compliant with hospital-based infliximab infusions and other medications, had no adverse events during hospital-based infliximab infusions, were in remission and had access to experienced pediatric homecare nursing. The children received 59 home infusions with a dose range of 7.5 to 10 mg/kg/dose. Home infusions ranged from 2 to 5 hours. Since infusions could be performed any day of the week, school absenteeism was decreased. The average patient satisfaction rating for home infusions was 9 on a scale from 1 to 10 (10 = most satisfied). Three patients experienced difficulty with IV access requiring multiple attempts, but all were able to receive their infusions. One infusion was stopped because of arm pain above the IV site. This patient had his next infusion in the hospital before returning to the home infusion program. No severe adverse events (palpitations, blood pressure instability, hyperemia, respiratory symptoms) occurred during home infusions. In the carefully selected patients, infliximab infusions administered at home were safe and are cost-effective. Patients and families preferred home infusions since time missed from school and work was reduced.

Several studies have demonstrated the safety of infusing a variety of infused medications in the home setting. Infusions of enzyme replacement therapies including agalsidase, elosulfase, galsulfase, iduronidase, idursulfase, velaglucerase have been demonstrated to be infused safely in the home. In addition, a self-administered formulation of belimumab is currently available, indicating the appropriateness of home administration. Alpha-1-antitrypsin therapy is generally considered safe and effective, exhibiting few and usually well tolerated side effects.

In a retrospective data analysis of over one thousand patients (N = 1,076) with primary immunodeficiency diseases (PIDD), Wasserman et al. (2017), examined the infection rates for patients who received IVIG at home or in a hospital outpatient infusion

center (HOIC). Patients were eligible for analysis if they had at least 1 inpatient or emergency room claim or at least 2 outpatient claims with a PIDD diagnosis from January 2002 and March 2013, 12 months of continuous health plan enrollment prior to index date (i.e., first IVIG infusion date), and 6 months of continuous IVIG at the same site of care after the index date. Incidences of pneumonia (bacterial or viral) and bronchitis (all types) within 7 days of IVIG infusion were retrospectively determined and compared between sites of care. Of the patients included in the analysis, 51% received IVIG in the home whereas 49% received it at an HOIC. The event/patient year of pneumonia was significantly lower in patients receiving IVIG at home compared to an outpatient hospital (0.102 vs. 0.216, P = 0.0071). The event/patient year of bronchitis was also significantly lower among patients infusing at home compared to an outpatient hospital (0.150 vs. 0.288, P < 0.0001). The authors concluded that patients with PIDD receiving IVIG in the home experienced significantly lower rates of pneumonia and bronchitis than those who received outpatient hospital based IVIG treatment. The lower infection rates in the home setting suggest that infection risk may be an important factor in site of care selection. The study is further limited by its observational nature.

The Immune Deficiency Foundation surveyed 1,030 patients on where they were treated with immune globulin. Twenty-six percent usually received infusions at a hospital outpatient department (21%) or at a hospital clinic (5%). Other sites reported included a doctor's private office (9%) or an infusion suite (16%). The most common site was in the home (42%), most administered by a nursing professional. (2008)

Clinical Practice Guidelines

American Academy of Allergy Asthma and Immunology (AAAAI)

The American Academy of Allergy Asthma and Immunology has published guidelines for the suitability of patients to receive treatment in various care setting including clinical characteristics of patients needing a high level of care in the hospital outpatient facility which includes patient characteristics: previous serious infusion reaction such as anaphylaxis, seizure, myocardial infarction, or renal failure, immune globulin therapy naïve, continual experience of moderate or serious infusion related adverse reactions, physical or cognitive impairment.

AAAAI treatment guidelines provide several site of care options for administering immune globulin, with the appropriate option being based on the patient's clinical condition:

- Hospital inpatient physician/nurse supervised infusion
- Hospital outpatient physician/nurse supervised infusion
- Physician office-based physician/nurse supervised infusion
- Home based infusion with nurse supervision
- Home based infusion without nurse supervision

The guidelines provide guidance on specific situation that may require a higher level of supervision, such as initial infusion of IVIG, changes in IVIG products, and specific clinical situations. (AAAAI., 2011)

AAAAI Guidelines for IGIV site of administration:

- All initial infusions of IGIV should be administered under physician supervision in a facility equipped to manage the most severe acute medical complications
- Changes in IGIV products should be provided under physician supervision in a facility prepared to manage the most severe acute medical complications
- Certain individuals continue to need higher levels of supervision and intervention throughout IGIV infusions
- Individuals who have tolerated IGIV therapy without a history of adverse events may be considered for lower levels of supervision during infusions
- Given the options for providing IGIV therapy, specific patient experiences command or exclude specific sites of care

(AAAI., 2011)

Hunter Syndrome European Expert Council

European recommendations for the diagnosis and multidisciplinary management of a rare disease published an article reviewing the collective experiences with agalsidase beta home infusion therapy and outlines how safe, patient-centered homecare can be organized in enzyme replacement therapy for patients with Fabry disease. Criteria include that "Patients must have received ERT in hospital for 3-6 months; if patients have previously had IRRs, they must be under control with premedication, and they must not have had an IRR in the 2-8 weeks before homecare is approved and premedication must be

given. If a patient has significant respiratory disease (%FVC, 40% or less; or evidence of serious obstructive airway disease), homecare may not be suitable."

Agency for Healthcare Research and Quality (AHRQ)

The AHRQ publication on Enzyme Replacement Therapy states, "Home infusion of ERT was initially studied in patients with type I Gaucher disease. It has been reported as an option for patients with Fabry disease, MPS I, and MPS II, and MPS VI. However, patients with infantile Pompe disease may not be able to transfer to home care because of an increased risk for serious adverse events during an infusion. In general, the outcomes measured in these studies and the follow-up durations were similar to those reported by disease in the clinical studies summarized under Guiding Question 3. Safety was the main focus of most home infusion studies, as the patients had already been receiving ERT in a more controlled setting."

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Guideline History/Revision Information

Date	Summary of Changes
04/01/2024	• Routine review; no change to coverage guidelines • Archived previous policy versions MMG141.AE

Instructions for Use

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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