Payer Denials and Appeals Resource

To Support Patients' Access to Takeda Immune Globulin Therapies

Takeda

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HOME

Introduction

The purpose of this resource is to equip healthcare providers (HCPs), institutions, specialty pharmacy providers (SPPs), and home infusion pharmacies with information to help respond to denials for immune globulin (IG) coverage. This resource includes brief explanations of some common reasons for coverage denial, a checklist for information to include when appealing specific denials, and specific references to support treatment with a Takeda IG product. The information included in this resource is meant to help navigate the appeals process for the use of the Takeda IG portfolio. Please note that third-party payment for medical products and services is affected by numerous factors, and Takeda cannot promise success in obtaining insurance payments for IG.

Takeda IG Products	Indications and Limitation of Use
Cuvitru [Immune Globulin Subcutaneous (Human)] 20%	CUVITRU, GAMMAGARD LIQUID, and GAMMAGARD S/D are indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients ≥2 years.
HyQvia [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]	HYQVIA is indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients two years of age and older. Safety and efficacy of chronic use of Recombinant Human Hyaluronidase in HYQVIA have not been established in conditions other than PI.
GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10%	CUVITRU and HYQVIA are for subcutaneous use only.
	GAMMAGARD LIQUID is for intravenous and subcutaneous use.
GAMMAGARD S/D [Immune Globulin Intravenous (Human)] IgA less than 1 µg/mL in a 5% solution	GAMMAGARD S/D is for intravenous use only.

IMPORTANT SAFETY INFORMATION

WARNING: THROMBOSIS

CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D

- **Thrombosis may occur with immune globulin (IG) products, including CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.**
- **For patients at risk of thrombosis, administer CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration.**
- **Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.**

WARNING: RENAL DYSFUNCTION and ACUTE RENAL FAILURE

GAMMAGARD LIQUID and GAMMAGARD S/D

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products, including GAMMAGARD LIQUID and GAMMAGARD S/D. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMMAGARD LIQUID and GAMMAGARD S/D do not contain sucrose.**

Please see Full Indication and Important Safety Information on pages 23-25 and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

Prior Authorization (PA)

PA is a management tool that requires the prescribing physician to justify the clinical need and therapeutic rationale for the prescribed medication before the health plan will process the prescription or reimburse the claim.[5] There are a number of reasons why a drug may require prior authorization, including:

- A need for additional clinical patient information to determine if coverage is appropriate[5]
- Prevention of drug misuse or inappropriate use[5]
- Administration of step therapy[5] **(click here for more information)**
- Administration of quantity limits or management rules[5]
- Exception process for a closed formulary[5] **(click here for more information)**

When a PA is required, the prescribing physician may submit the PA directly to the payer or the pharmacy may complete the PA on behalf of the prescriber before the plan will cover the medication.

PA criteria vary from plan to plan; however, the following criteria are commonly found across top payer types and may be required for IG therapy. These criteria should be considered when drafting a PA request form:

- Physician specialty (i.e., allergist/immunologist)[6]
- Laboratory evidence of immunoglobulin deficiency[7]
  - IgG <200 mg/dL is a common minimum target for PI diagnosis.[7,8] In patients with mild to moderate IgG deficiency with levels of 300 mg/dL-400 mg/dL, the decision to treat is based on clinical symptoms and vaccine challenge
- Laboratory evidence of inability to mount an adequate response to inciting antigens[7,8]
  - Titers need to be drawn from patient before challenging with vaccination and again 4 to 8 weeks after vaccination to demonstrate lack of response[7,8]
  - For example, an adequate response to the pneumococcal vaccine may be defined as at least a 4-fold increase in titers for at least 50% of serotypes tested[7]
- Patient has a history of multiple hard-to-treat infections, which may be indicated by at least one of the following[8]:
  - Four or more ear infections within 1 year
  - Two or more serious sinus infections within 1 year
  - Two or more months of antibiotics with little effect
  - Two or more pneumonias within 1 year
  - Recurrent or deep skin abscesses
  - Need for intravenous (IV) antibiotics to clear infections
  - Two or more deep-seated infections, including septicemia

Unfortunately, a PA request may not always be approved.

In this scenario, the prescribing physician will need to prepare additional information to appeal the decision. There are numerous reasons why a PA could be denied, some of which are described below, but a common reason for PA denial is incomplete information. It is crucial for the physician or specialty pharmacy completing the PA request to include all relevant diagnostic and patient information, including the prescribing physician's case notes. When a PA request is denied, whether for incomplete information or a different reason, an appeal will need to include additional support for why the medication is clinically necessary for the patient, and be submitted in the time frame specified by the patient's insurance.

Click here for PA request form checklist

Click here for PA appeals letter checklist

Step Therapy

Step therapy, or fail-first, is a management tool frequently included in a PA that requires a trial of one or more preferred medications before a non-preferred medication is covered. In IG, there are 2 kinds of step therapy that could affect a patient's access to their prescribed medication.

1. Some plans may require trial and failure of a 5% or 10% IG product before covering a 20% IG product or require use of a 10% IG product that may be IV or SC before covering a subcutaneous IG (SCIG)-only product.
2. Step through a preferred product/preferred drug list (PDL) – Plan might have preferred IG products that a patient must try and fail before a different, non-preferred option is covered.

A prior authorization denial due to step therapy may be appealed. Some plans require a **letter or statement of medical necessity (LMN, SMN)** to be submitted along with the PA appeals letter to support the IG product choice.

Click here for **PA appeals letter checklist**

Click here for **LMN/SMN checklist**

Click here for **supporting references table**

Formulary Exclusion

There are 2 basic types of formularies a health plan can have.

1 Open[5]

An open formulary pharmacy benefit provides coverage at the point of sale for all medications covered under the prescription benefit, even those not listed on the formulary.[5]

2 Closed[5]

Under a closed formulary pharmacy benefit, only the drugs listed on the formulary are covered at the point of sale.[5] Nonformulary medications can only be obtained via a formulary exception process.

The PA process can be used to request coverage for Takeda IG products that are covered under the pharmacy benefit but are not included on a plan's formulary. A formulary exception request form prepared by the prescribing physician should be submitted to the patient's health plan as part of this process.

Note: Restricted formularies may also be available whereby coverage is contingent on a set of criteria. See the "Prior Authorization" section starting on page 4 for more information.

Click here for the formulary exception request form checklist

Site of Care Requirement

Some health plans have a site-of-care policy for specific injectable or infused drugs. For the initial infusion of IG, reinitiation of IG therapy after more than 6 months off therapy, or the change of an IG product, health plans will generally cover the physician's site of care of choice, including a hospital.[9,10] For subsequent infusions, health plans may not cover infusions in the hospital setting unless the physician provides evidence of medical necessity.[9,10] Health plans will have their own specific site-of-care policies, but in general, it may be considered medically necessary for patients receiving IG to receive their infusion in an outpatient hospital or in a home care setting if one or more of the following criteria are met:

- History of severe adverse reactions to IG[9,10]
- Patient has an immunoglobulin A (IgA) deficiency with anti-IgA antibodies[9,10]

If the site of care that the patient and the patient's physician have agreed upon is not covered by the patient's insurance, it may be necessary to submit an LMN/SMN outlining the reasons why the chosen site of care is medically necessary.

Click here for LMN/SMN checklist

Click here for supporting references table

Coding Error

If the incorrect diagnosis code, national drug code (NDC), Healthcare Common Procedures Coding System (HCPCS) code, or Current Procedural Terminology (CPT®) code is submitted in the claim, the claim may be denied.[11] The prescribing physician will then have to identify the correct code before reopening the claim, possibly delaying a patient's access to necessary medication.

To help prevent coding errors, Takeda provides coding guides for all of the IG products in its portfolio.

Click here for billing and coding information

Out-of-Network Pharmacy

If the physician sends the prescription for a Takeda IG product to a pharmacy that is not in the plan's specialty pharmacy network, the claim will not be processed. The out-of-network pharmacy may contact the provider's office to note the issue or may transfer the prescription to an in-network pharmacy directly. The out-of-network pharmacy may also get an exception to fill the prescription and patient may choose to pay out of pocket if approved to dispense. Health plans may provide information on preferred specialty pharmacies in provider newsletters or via publication of specialty drug lists.

High-Dollar-Amount Edits

All IG products require weight-based dosing, leading to a large variation in cost from patient to patient. Patients that require a larger amount of IG may experience a delay in their claim approval due to a high-dollar-amount edit. This issue may be resolved with the submission of an LMN/SMN that includes details such as the patient's height and weight, and information from the FDA label or treatment guidelines to support why the prescribed dose is appropriate.

Click here for LMN/SMN checklist

Click here for supporting references table

Incorrect Benefit

Takeda's IG portfolio includes IVIG and SCIG products, and there is some variance in how the different products are billed to commercial health plans. IVIG products and the associated support staff and medical equipment are generally covered under the medical benefit. For SCIG, the product itself is usually covered under the pharmacy benefit, but other items necessary for administration may be covered under the medical benefit. Additionally, the initial dose of a Takeda SCIG product may be administered in a hospital outpatient facility or an infusion center, in which case the product itself may be covered under the medical benefit. A home nursing visit to assist with administration may also be covered under the medical benefit.

If a patient's claim is rejected due to billing to the incorrect benefit, the HCP should work with the dispensing pharmacy to correct the error and the dispensing pharmacy should resubmit the claim to the appropriate benefit.

Medicare-Specific Reimbursement Challenges

IG therapy for PI, whether it is IVIG or SCIG, is ~80% covered under Medicare Part B.[12] If the IVIG/SCIG service claim is submitted under Part D when it should be under Part B, the HCP will need to resubmit the claim through the appropriate benefit.[13]

The following conditions must be met for IVIG and SCIG to be covered under Medicare Part B in the home setting[14]:

- Patient is diagnosed with PI
- Physician determines that administration of IVIG in the home is medically appropriate

It is important to note that Medicare Part B does not include coverage for items or services related to IVIG administration (ie, nursing professionals for at-home IVIG administration).[14]

The following diagnosis codes are approvable under Medicare Part B[14]:

ICD-10[15]	
G11.3	Cerebellar ataxia with defective DNA repair
D80.0	Hereditary hypogammaglobulinemia
D80.2	Selective deficiency of immunoglobulin A [IgA]
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased IgM
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D81.0	SCID with reticular dysgenesis
D81.1	SCID with low T- and B-cell numbers
D81.2	SCID with low or normal B-cell numbers
D81.5	Purine nucleoside phosphorylase (PNP) deficiency
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified; SCID NOS
D82.0	Wiskott-Aldrich syndrome
D82.1	Di George's syndrome
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified

ICD, International Classification of Diseases; NOS, not otherwise specified; SCID, severe combined immunodeficiency.

For detailed information on the Medicare appeals process for drugs covered under Part B and Part D, please refer to the official Medicare Appeals booklet **https://www.medicare.gov/sites/default/files/2018-07/11525.pdf**.

PA Request Form Checklist

- O Be sure to fill in as much information on the form as possible. Incomplete information can lead to a PA denial
- O Include the patient's name, policy number, ID number, group number, and date of birth
- O Include the prescribing physician's name, specialty, and NPI number
- O Include the phone numbers for the prescribing physician and patient if the health plan requires any additional information to support the appeal
- O Include specific billing codes where appropriate
  - O Include the ICD-10 code and relevant HCPCS code and NDC code, if applicable
- O If the patient is currently receiving an IG product, include the product name, manufacturer name, and dose
  - O Include specific measures of clinical benefit seen in the patient with the IG product
- O Include the prescribed dose and patient weight
- O If the PA includes preferred products, include content from the Additional considerations for a formulary exception request form
- O Include additional clinical information, if applicable
  - O Clinical diagnosis
  - O Laboratory results
    - O Complete Blood Count (CBC) with differential
    - O Total immunoglobulin levels (IgG, IgM, IgA)
    - O Pre- and post-vaccination titers (if requested)
    - O Genetic testing confirming the diagnosis, if applicable
  - O Physician's case notes
    - O Family history of PI
    - O Control of underlying conditions, such as asthma or allergic rhinitis
  - O History of infections and antibiotics
    - O Hospitalizations due to infection
  - O Previous therapies and response
- O If requested, include the patient's medical records and all of the documents listed or referenced in the PA request form when it is sent to the patient's insurance provider
- O Signature from the prescribing physician

Additional Considerations for a PA Appeals Letter

In addition to the information listed in the **PA request form checklist**, consider including the following items in a PA appeals letter:

- O Review the reason for the denial, if supplied
  - O If information (dose, indicated use, etc) was missing from original PA request that may have led to the denial, include that information in the appeal
- O Confirm the timeline and process for appeals
- O Confirm where the appeal is to be sent; it may differ from the original PA request
- O Provide well-accepted diagnostic studies and standards of practical criteria to support the laboratory studies, if applicable
- O Include a letter or statement of medical necessity if required by the patient's health plan
- O Include the names of immunologists that have completed the scientific research on the diagnosis in question, should the health plan request a peer review

Click here for supporting references table

Please do not share with your Takeda representative any documentation of labs, clinical history, or other patient-specific information.

Appeals Review

Consider the following to help prepare for a successful peer-to-peer review in the appeal process:

- Clinical rationale supported by medical history or publications are the most compelling, but quality of life rationale may also be considered
- Submit a letter or statement of medical necessity in writing prior to the peer-to-peer review
- Request a like specialist (e.g., allergist/immunologist, clinical immunologist)
- Refer to and have relevant documents and lab results available during the discussion (e.g., diagnosis, case notes, medical history)
- Refer to supporting references and publications to support rationale for a particular product
- Discuss the results of a successful trial of product, if available
- Discuss the potential consequences of a denial for the patient
- Discuss patient's adverse events with previously trialed products, if appropriate
- Be available during the call window; missing the peer-to-peer review can result in automatic denials
- If denial is the final outcome of the review, ask for the peer's name and license number to be noted in the chart

Additional Considerations for a Formulary Exception Request Form

In addition to the information listed in the **PA request form checklist**, consider including the following items in a formulary exception request form:

- Be sure to fill in as much information on the form as possible. Incomplete information can lead to a denial
- Clearly state the rationale for prescribing an IG product that is not on formulary and why the formulary agents are not appropriate. Possible reasons include:
  - Patient comorbidities
  - Previous infusion-related adverse reactions
  - Patient is currently stable on drug that is not on formulary
  - Limited availability of formulary alternatives
  - Prior therapeutic failure on formulary agent
  - Volume limitations
  - Hypersensitivity to formulary agents or components therein

Click here for supporting references table

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Letter or Statement of Medical Necessity (LMN, SMN)

An LMN/SMN is a critical component of appealing a coverage denial or requesting a formulary exception. The LMN/SMN is the prescribing physician's opportunity to present all of the rationale for why a certain Takeda IG product is clinically necessary for the patient. It is important to note that LMN/SMNs should be concise while making as strong an argument as possible, and should be drafted on official letterhead stationery.

In addition to the information listed in the **PA request form checklist**, consider including the following items in an LMN/SMN:

- Clearly state the rationale for treatment with the relevant Takeda IG product and why it is appropriate for the patient
  - Include support for the treatment recommendation
    - Citing published trials can be impactful. See the updated guidelines on the use of immunoglobulin in human disease
  - Specify if patient is already on a Takeda IG product and is clinically stable and include specific measures of clinical benefit
  - Explain why the formulary-preferred agents, if applicable, are not appropriate (eg, patient's comorbidities, previous infusion-related adverse reaction, etc)
  - Outline implications if patient goes without treatment
- If applicable, include the product name, duration of treatment, and reason for discontinuation for any previous IG treatments

Click here for supporting references table

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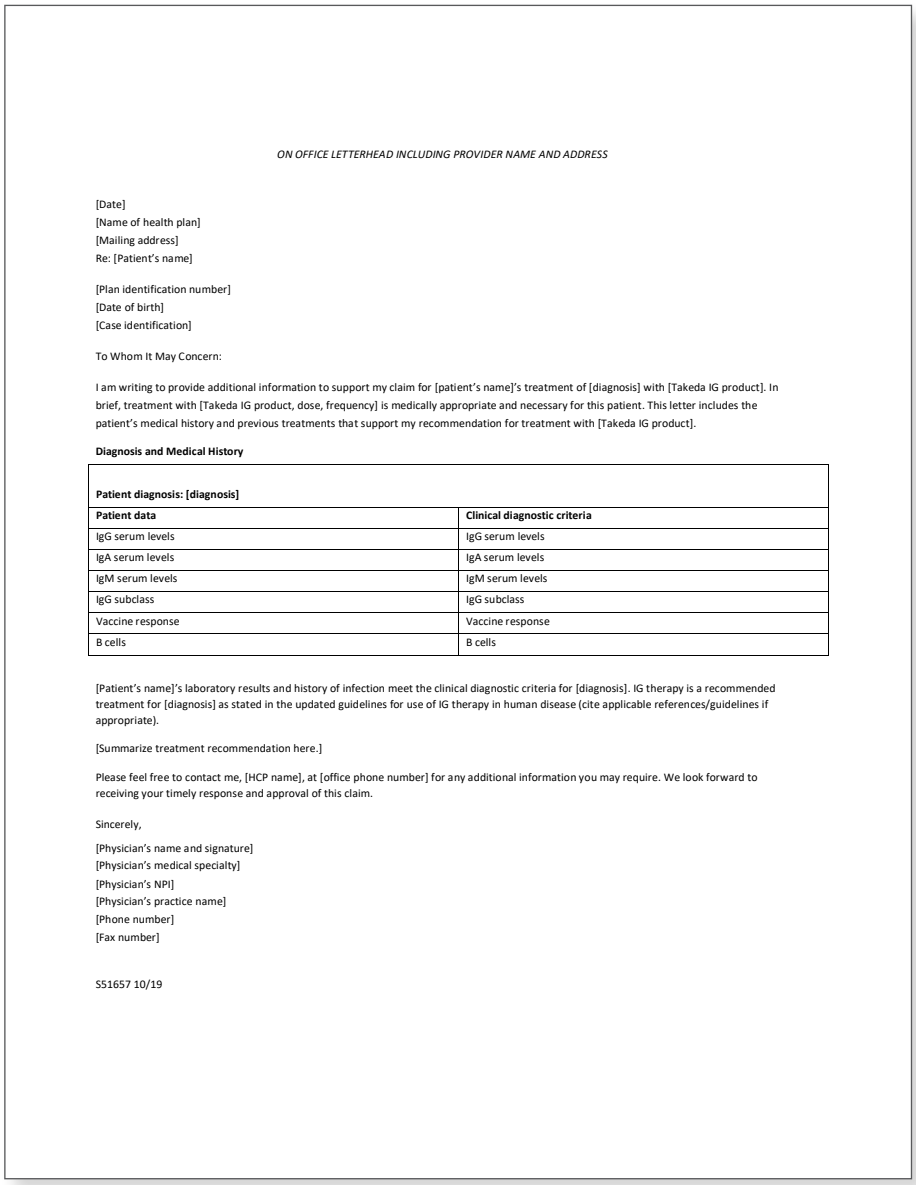
Letter or Statement of Medical Necessity (LMN, SMN) (cont'd)

Important information to consider including in a LMN/ SMN letter when prescribing Takeda IG products not on formulary or on the preferred drug list:

- Evidence of clinical benefit seen with Takeda IG treatment. Can include pre- and post-treatment laboratory results in the above table to demonstrate clinical benefit
- Patient-specific reasons for prescribing an IG product that is not preferred or on formulary (patient comorbidities, history of adverse reactions to formulary agent, etc)
- Rationale against switching IG products
- Reasons why IG products are not interchangeable
- Clinical implications if treatment with the Takeda IG product is interrupted
- For patients prescribed SCIG, include rationale for SCIG treatment
- For patients whose chosen site of care is not covered, include rationale to support site of care



ON OFFICE LETTERHEAD INCLUDING PROVIDER NAME AND ADDRESS

[Date]
[Name of health plan]
[Mailing address]
Re: [Patient's name]

[Plan identification number]
[Date of birth]
[Case identification]

To Whom It May Concern:

I am writing to provide additional information to support my claim for [patient's name]'s treatment of [diagnosis] with [Takeda IG product]. In brief, treatment with [Takeda IG product, dose, frequency] is medically appropriate and necessary for this patient. This letter includes the patient's medical history and previous treatments that support my recommendation for treatment with [Takeda IG product].

Diagnosis and Medical History

Patient diagnosis: [diagnosis]

Patient data	**Clinical diagnostic criteria**
IgG serum levels	IgG serum levels
IgA serum levels	IgA serum levels
IgM serum levels	IgM serum levels
IgG subclass	IgG subclass
Vaccine response	Vaccine response
B cells	B cells

[Patient's name]'s laboratory results and history of infection meet the clinical diagnostic criteria for [diagnosis]. IG therapy is a recommended treatment for [diagnosis] as stated in the updated guidelines for use of IG therapy in human disease (cite applicable references/guidelines if appropriate).

[Summarize treatment recommendation here.]

Please feel free to contact me, [HCP name], at [office phone number] for any additional information you may require. We look forward to receiving your timely response and approval of this claim.

Sincerely,

[Physician's name and signature]
[Physician's medical specialty]
[Physician's NPI]
[Physician's practice name]
[Phone number]
[Fax number]

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Click here for supporting references table

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Support References

Please refer to the below support information for treatment with a Takeda IG product, which may be included in a PA request form or appeals letter, an LMN/SMN, or a formulary exception request form to further support the case.

Support	Reference Citation
Support for Indication/Appropriate Use of IG	
Recommendations and rationale for use of IG in specific disease states are included in the updated guidelines on the use of IG in human disease	Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol*. 2017;139(3 suppl):S1-S46. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/IVIG-March-2017.pdf**.
A summary of disease-specific diagnostic criteria can be found in the 2015 practice parameter for the diagnosis and management of PI	Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015;136(5):1186-1205. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/PID-Nov-2015.pdf**.
Rationale Against Switching IG Products	
Significant adverse reactions occur in ~15%-18% of patients when switching IVIG products	Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol*. 2017;139:S1-S46. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/IVIG-March-2017.pdf**.
The *AAAAI Guiding Principles* state that a patient stabilized on a particular product should be maintained on that particular therapy	American Academy of Allergy, Asthma & Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf**. December 2011. Accessed October 2, 2019.
Reasons Why IG Products Are Not Interchangeable	
The *AAAAI Guiding Principles* state that the various IG products that are indicated for the treatment of PI diseases "are not generic and there are notable differences amongst them" • A patient with diabetes should not use an IG product that uses glucose as a stabilizer • IG products with a higher sodium content would not be appropriate to use in patients with cardiac conditions	American Academy of Allergy, Asthma & Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf**. December 2011. Accessed October 2, 2019.
IG products are not interchangeable, and patients can have varying reactions to seemingly similar products. The 2013 IDF treatment survey found that 60% of PI patients who have been on more than one IG product tolerate some IG products better than others	Immune Deficiency Foundation. 2013 IDF national immunoglobulin treatment survey. **https://www.primaryimmune.org/sites/default/files/2013_IDF_National_Immunoglobulin_Treatment_Survey.pdf**. Accessed October 2, 2019.
Patient tolerance or responsiveness can vary across IG products. Treating patients with a poorly tolerated IG therapy can result in higher costs due to the likelihood of additional required treatments. From a cost-effectiveness perspective, the evidence suggests that physicians should have the flexibility to choose the most appropriate therapy for their patients based on an individual's unique conditions and tolerability profile	Grabowski H, Manning R. Key economic and value considerations in the U.S. market for plasma protein therapies. Bates White Economic Consulting. February 2018. **https://www.bateswhite.com/media/publication/154_Plasma_Protein_Therapies_paper.pdf**. Accessed October 2, 2019.

Support References (cont'd)

Support	Reference Citation
Rationale to Support SCIG	
Subcutaneous IG therapy presents numerous benefits for patients experiencing severe or difficult to control adverse events related to intravenous IG infusion **NOTE:** The physician may need to list patient-specific benefits of SCIG therapy and include documentation of the adverse events to demonstrate clinical need	American Academy of Allergy, Asthma & Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf**. December 2011. Accessed October 2, 2019.
Patients with poor venous access may require SCIG **NOTE:** The physician will need to provide documentation of the reason for poor venous access (ie, type of VAD, prior VAD infections, etc)	American Academy of Allergy, Asthma & Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf**. December 2011. Accessed October 2, 2019.
Because patients have steady-state serum IgG levels with SCIG, they experience minimal withdrawal effects, such as malaise or symptoms of infection, in the week prior to the next IVIG infusion. **NOTE:** The physician may need to provide documentation and attest to the patient's withdrawal symptoms	Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol*. 2017;139:S1-S46. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/IVIG-March-2017.pdf**.
Rationale to Support IVIG Site of Care	
Certain patients require higher levels of monitoring and intervention during IVIG infusions. If infusion-related adverse events are anything but mild, physician supervision should be available. **NOTE:** The physician will also need to include patient-specific information to demonstrate clinical need for increased monitoring	American Academy of Allergy, Asthma & Immunology. Guidelines for site of care for administration of IVIG therapy. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/Guidelines-for-the-site-of-care-for-administration-of-IGIV-therapy.pdf**. Accessed October 2, 2019.
Some patients with PI may require frequent follow-up visits with physicians because of disease-related complications (chronic bronchitis, irritable bowel disease, etc) or to ensure appropriate management of the underlying disease. In some cases, considerable savings in time and costs can be achieved by having physician follow-up visits at the same time and place as the IVIG infusions.	American Academy of Allergy, Asthma & Immunology. Guidelines for site of care for administration of IVIG therapy. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/Guidelines-for-the-site-of-care-for-administration-of-IGIV-therapy.pdf**. Accessed October 2, 2019.
Rationale to Support Prescribed Dose	
Defining "adequate" treatment or IG dosing with the standard of minimal or suboptimal IgG levels can potentially harm patients. Treatment regimens and dosing should be individualized for each patient.	Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol*. 2017;139:S1-S46. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/IVIG-March-2017.pdf**.
For patients switching from IVIG to SCIG, dose may need to be adjusted beyond the conversion factor of 1.37 for patients with a very low or very high BMI. Studies of 16% and 20% SCIG formulations have suggested that subjects with a high BMI might require higher dose adjustments when switching for IVIG to SCIG.	Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol*. 2017;139:S1-S46. **https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/IVIG-March-2017.pdf**.

AAAAI, American Academy of Allergy, Asthma & Immunology; IDF, Immune Deficiency Foundation; VAD, vascular access device.

This is not an exhaustive list of references that may be helpful to support treatment with a Takeda IG product in the context of a denial and appeal or formulary exception request.

Each insurer and/or patient may need different information to support the appeal or formulary exception process. Carefully review the insurer guidelines and denial, if applicable, to determine what information should be included in your submission.

PI ICD-10 Diagnosis Codes[15]

CUVITRU [Immune Globulin Subcutaneous (Human)] 20%, HYQVIA [Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase], GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10%, and GAMMAGARD S/D [Immune Globulin Intravenous (Human)] IgA less than 1 μg/mL in a 5% solution

D80	Immunodeficiency With Predominantly Antibody Defects
D80.0	Hereditary hypogammaglobulinemia Autosomal recessive agammaglobulinemia (Swiss type) X-linked agammaglobulinemia [Bruton] (with growth hormone deficiency)
D80.1	Nonfamilial hypogammaglobulinemia Agammaglobulinemia with immunoglobulin-bearing B-lymphocytes Common variable agammaglobulinemia [CVAgamma] Hypogammaglobulinemia NOS
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D80.8	Other immunodeficiencies with predominantly antibody defects Kappa light chain deficiency
D80.9	Immunodeficiency with predominantly antibody defects, unspecified

D82	Immunodeficiency Associated With Other Major Defects
D82.0	Wiskott-Aldrich syndrome Immunodeficiency with thrombocytopenia and eczema
D82.1	Di George's syndrome Pharyngeal pouch syndrome Thymic alymphoplasia Thymic aplasia or hypoplasia with immunodeficiency
D82.2	Immunodeficiency with short-limbed stature
D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus X-linked lymphoproliferative disease
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D82.8	Immunodeficiency associated with other specified major defects
D82.9	Immunodeficiency associated with major defect, unspecified

D81	Combined Immunodeficiencies
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.4	Nezelof's syndrome
D81.6	Major histocompatibility complex class I deficiency Bare lymphocyte syndrome
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified Severe combined immunodeficiency disorder [SCID] NOS

D83	Common Variable Immunodeficiency
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified

IMPORTANT SAFETY INFORMATION (cont'd)

Contraindications

- **CUVITRU**, **HYQVIA**, and **GAMMAGARD LIQUID** are contraindicated in patients with a history of anaphylactic or severe systemic hypersensitivity reactions to human IG, and IgA-deficient patients with antibodies to IgA and a history of hypersensitivity to human IG. Anaphylaxis has been reported with intravenous (IV) use of **GAMMAGARD LIQUID**.
- Additionally, **HYQVIA** is contraindicated in patients with known systemic hypersensitivity to hyaluronidase including Recombinant Human Hyaluronidase of **HYQVIA**, and known systemic hypersensitivity to human albumin (in the hyaluronidase solution).
- **GAMMAGARD S/D** is contraindicated in patients with a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of **GAMMAGARD S/D**.

Warnings and Precautions

Hypersensitivity: Severe hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with human IG. Severe hypersensitivity reactions and anaphylactic reactions with a fall in blood pressure have occurred in patients receiving **GAMMAGARD S/D**, including patients who tolerated previous treatments with **GAMMAGARD S/D**, even though it contains low levels of IgA. If a hypersensitivity reaction occurs, discontinue infusion immediately and institute appropriate treatment. IgA-deficient patients with antibodies to IgA are at greater risk of developing potentially severe hypersensitivity reactions, including anaphylaxis.

Renal Dysfunction/Failure: Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur with IV use of IG products, especially those containing sucrose. Acute renal failure has been reported in association with **GAMMAGARD LIQUID** and **GAMMAGARD S/D**. Ensure patients are not volume depleted prior to infusion. In patients at risk due to pre-existing renal insufficiency or predisposition to acute renal failure, assess renal function before initiation and throughout treatment, and consider lower, more frequent dosing. If renal function deteriorates, consider discontinuation.

Please see Full Indication and Important Safety Information on pages 23-25 and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

CUVITRU Billing Codes

The provider is responsible for ensuring accurate and appropriate diagnostic coding to obtain reimbursement.

Applicable HCPCS Codes[16]	
HCPCS Code	**Description**
J1555	Injection, immune globulin (CUVITRU), 100 mg
DME and Supply Codes	
HCPCS Code	**Description**
External Infusion Pump	
E0779	Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater
E0780	Ambulatory infusion pump, mechanical, for infusion less than 8 hours
E0781	Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient
E0791	Parenteral infusion pump, stationary, single, or multichannel
External Infusion Pump Supplies	
A4221	Supplies for maintenance of drug infusion catheter, per week (list drugs separately)
A4222	Infusion supplies for external drug infusion pump, per cassette or bag
K0552	Supplies for external drug infusion pump, syringe type cartridge, sterile, each

CUVITRU NDC Numbers[1]			
NDC Number		**Grams Protein** [Immune Globulin Subcutaneous (Human) 20%]	**J1555-Billing Units** [Injection, immune globulin (CUVITRU), 100 mg]
0944-2850-01	5 mL	1.0	10 units
0944-2850-03	10 mL	2.0	20 units
0944-2850-05	20 mL	4.0	40 units
0944-2850-07	40 mL	8.0	80 units
0944-2850-09	50 mL	10.0	100 units

CPT Codes[17]

Subcutaneous Administration

The following CPT codes apply to administration services performed by a healthcare provider concurrent with infusion.

CPT Code	Description
96369	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s)
96370	Each additional hour (list separately in addition to code for primary procedure)

CPT, Current Procedural Terminology; DME, durable medical equipment; HCPCS, Healthcare Common Procedure Coding System; NDC, national drug code.

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Third-party payment for medical products and services is affected by numerous factors, and Takeda cannot guarantee success in obtaining insurance payments. This Coding Reference Guide is current as of August 2019.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Thrombosis: Has been reported to occur following treatment with IG products, including **HYQVIA** and in the absence of known risk factors. In patients at risk, administer at the minimum dose and infusion rate practicable. Ensure adequate hydration before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Please see Full Indication and Important Safety Information on pages 23-25 and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

HyQvia
[Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]

HYQVIA Billing Codes

The provider is responsible for ensuring accurate and appropriate diagnostic coding to obtain reimbursement.

HYQVIA HCPCS Code[16]

HCPCS Code	Description
J1575	Injection, immune globulin/hyaluronidase, (HYQVIA), 100 mg immune globulin
DME and Supply Codes	
HCPCS Code	**Description**
E0779	Ambulatory infusion pump, mechanical, reusable, for infusion of 8 hours or greater
E0780	Ambulatory infusion pump, mechanical, for infusion less than 8 hours
E0781	Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient
E0791	Parenteral infusion pump, stationary, single, or multichannel
A4221	Supplies for maintenance of drug infusion catheter, per week (list drugs separately)
K0552	Supplies for external drug infusion pump, syringe type cartridge, sterile, each
Home Infusion Therapy	
HCPCS Code	**Description**
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

CPT Codes[17]

Subcutaneous Administration	
96369	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s)
96370	Each additional hour (list separately in addition to code for primary procedure)
96371	Additional pump set-up with establishment of new subcutaneous infusion site(s) (list separately in addition to code for primary procedure)

NDC Numbers[2]

NDC Number	Volume	Grams Protein [Immune Globulin 10% (Human)]	J1575-Billing Units[a] [Injection, immune globulin/ hyaluronidase, (HYQVIA) 100 mg immune globulin]
0944-2510-02	25 mL	2.5	25 mL
0944-2511-02	50 mL	5.0	50 mL
0944-2512-02	100 mL	10.0	100 mL
0944-2513-02	200 mL	20.0	200 mL
0944-2514-02	300 mL	30.0	300 mL

[a]HYQVIA is supplied in a dual-vial unit of 2 single-use vials containing the labeled amount of functionally active Immune Globulin Infusion 10% (Human) and Recombinant Human Hyaluronidase.

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IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Aseptic Meningitis Syndrome: Has been reported with use of IG, including **HYQVIA** and may occur more frequently in females. Conduct a thorough neurological exam on patients exhibiting signs and symptoms, to rule out other causes of meningitis. Discontinuing IG treatment has resulted in remission within several days without sequelae. The syndrome usually begins within several hours to two days following IG treatment.

Hemolysis: **CUVITRU**, **HYQVIA**, **GAMMAGARD LIQUID**, and **GAMMAGARD S/D** contain blood group antibodies, which may cause a positive direct antiglobulin reaction and hemolysis. Monitor patients for signs and symptoms of hemolysis and delayed hemolytic anemia and, if present, perform appropriate confirmatory lab testing.

Please see Full Indication and Important Safety Information on pages 23-25 and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

Takeda

GAMMAGARD LIQUID Billing Codes

GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10%

The provider is responsible for ensuring accurate and appropriate diagnostic coding to obtain reimbursement.

HCPCS Codes[16] [Immune Globulin Infusion (Human)] 10%

HCPCS Code	Description
J1569[a]	Injection, immune globulin (GAMMAGARD LIQUID), intravenous, non-lyophilized (eg, liquid), 500 mg
J1569JB[b]	

[a]The HCPCS code currently assigned to GAMMAGARD LIQUID, J1569, only describes the intravenous route of administration. Providers are advised to contact the payer for the appropriate HCPCS code when GAMMAGARD LIQUID is administered subcutaneously.

[b]Medicare DME MAC coding guidance for GAMMAGARD LIQUID with the subcutaneous route of administration via a pump.

Home Infusion Therapy (for IVIG or SCIG)[16]

HCPCS Code	Description
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

Healthcare providers should contact payers for guidance on appropriate coding.

NDC Numbers[3]

NDC Number	Grams
0944-2700-02	1.0
0944-2700-03	2.5
0944-2700-04	5.0
0944-2700-05	10.0
0944-2700-06	20.0
0944-2700-07	30.0

Hospital Revenue Code

Code	Description
0636	Pharmacy, drugs requiring detailed coding

CPT Codes[17]

Intravenous Administration

CPT Code	Description
96365	IV infusion for therapy, prophylaxis, or diagnosis; initial, up to 1 hour
96366 (add-on code)	IV infusion for therapy, prophylaxis, or diagnosis; each additional hour (List separately in addition to code for primary procedure)
96367 (add-on code)	IV infusion for therapy, prophylaxis, or diagnosis; additional sequential infusion, up to 1 hour (List separately in addition to code for primary procedure)
96368 (add-on code)	IV infusion for therapy, prophylaxis, or diagnosis; concurrent infusion (List separately in addition to code for primary procedure)

Subcutaneous Administration

CPT Code	Description
96369	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s) Excludes infusions of 15 minutes or less (96372)
96370	Each additional hour (List separately in addition to code for primary procedure) Includes infusions of more than 30 minutes beyond 1 hour
96371	Additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure)

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IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Transfusion-Related Acute Lung Injury: Non-cardiogenic pulmonary edema may occur with IV administered IG. Monitor patients for pulmonary adverse reactions. If suspected, perform appropriate tests for presence of anti-neutrophil and anti-HLA antibodies in both product and patient serum. May be managed using oxygen therapy with adequate ventilatory support.

Transmittable Infectious Agents: Because **CUVITRU**, **HYQVIA**, **GAMMAGARD LIQUID**, and **GAMMAGARD S/D** are made from human plasma, they may carry a risk of transmitting infectious agents (e.g., viruses, other pathogens). No confirmed cases of viral transmission of variant Creutzfeldt-Jakob disease (vCJD) have been associated with **CUVITRU** or **GAMMAGARD LIQUID**, and no cases have been associated with **HYQVIA**.

Interference with Lab Tests: False positive serological test results and certain assay readings, with the potential for misleading interpretation, may occur as the result of passively transferred antibodies.

Additional Warnings and Precautions for HYQVIA

Immunogenicity of Recombinant Human Hyaluronidase (rHuPH20): Non-neutralizing antibodies to the Recombinant Human Hyaluronidase component can develop. The clinical significance of these antibodies or whether they interfere with fertilization in humans is unknown.

Spread of Localized Infection: Do not infuse **HYQVIA** into or around an infected area due to potential risk of spreading a localized infection.

Please see Full Indication and Important Safety Information on pages 23-25 and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

GAMMAGARD S/D
[Immune Globulin Intravenous (Human)]
IgA less than 1 µg/mL in a 5% solution

GAMMAGARD S/D Billing Codes[16]

The provider is responsible for ensuring accurate and appropriate diagnostic coding to obtain reimbursement.

HCPCS Codes and Descriptions[16]	
Drug-specific HCPCS Code	
J1566	Injection, immune globulin, intravenous, lyophilized (eg, powder), not otherwise specified, 500 mg
DME and Supply Codes	
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
CPT Codes and Descriptions[17]	
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (list separately in addition to code for primary procedure)
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (list separately in addition to code for primary procedure)
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (list separately in addition to code for primary procedure)

NDC Number[4]	Grams Protein
0944-2656-03	5 g
0944-2658-04	10 g

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Third-party payment for medical products and services is affected by numerous factors, and Takeda cannot guarantee success in obtaining insurance payments. This Coding Reference Guide is current as of August 2019.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Additional Warnings and Precautions for GAMMAGARD LIQUID and GAMMAGARD S/D

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur. It is critical to distinguish true hyponatremia from a pseudohyponatremia because certain treatments may lead to volume depletion, a further increase in serum viscosity, and a predisposition to thromboembolic events.

Alterations in serum sodium levels (i.e., acute hypernatremia, pseudohyponatremia) may occur with **GAMMAGARD S/D**. In patients on a low sodium diet, calculate the amount of sodium from **GAMMAGARD S/D** when determining dietary sodium intake.

Please see Full Indication and Important Safety Information on pages 23-25 and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

INDICATIONS AND LIMITATION OF USE

CUVITRU, **GAMMAGARD LIQUID**, and **GAMMAGARD S/D** are indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients ≥2 years.

HYQVIA is indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients two years of age and older. Safety and efficacy of chronic use of Recombinant Human Hyaluronidase in **HYQVIA** have not been established in conditions other than PI.

CUVITRU and **HYQVIA** are for subcutaneous use only.

GAMMAGARD LIQUID is for intravenous and subcutaneous use.

GAMMAGARD S/D is for intravenous use only.

IMPORTANT SAFETY INFORMATION

WARNING: THROMBOSIS

CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D

- **Thrombosis may occur with immune globulin (IG) products, including CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.**
- **For patients at risk of thrombosis, administer CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration.**
- **Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.**

WARNING: RENAL DYSFUNCTION and ACUTE RENAL FAILURE

GAMMAGARD LIQUID and GAMMAGARD S/D

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products, including GAMMAGARD LIQUID and GAMMAGARD S/D. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMMAGARD LIQUID and GAMMAGARD S/D do not contain sucrose.**

Contraindications

- **CUVITRU**, **HYQVIA**, and **GAMMAGARD LIQUID** are contraindicated in patients with a history of anaphylactic or severe systemic hypersensitivity reactions to human IG, and IgA-deficient patients with antibodies to IgA and a history of hypersensitivity to human IG. Anaphylaxis has been reported with intravenous (IV) use of **GAMMAGARD LIQUID**.
- Additionally, **HYQVIA** is contraindicated in patients with known systemic hypersensitivity to hyaluronidase including Recombinant Human Hyaluronidase of **HYQVIA**, and known systemic hypersensitivity to human albumin (in the hyaluronidase solution).
- **GAMMAGARD S/D** is contraindicated in patients with a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of **GAMMAGARD S/D**.

Please see Full Indication and Important Safety Information on next page and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

Hypersensitivity: Severe hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with human IG. Severe hypersensitivity reactions and anaphylactic reactions with a fall in blood pressure have occurred in patients receiving **GAMMAGARD S/D**, including patients who tolerated previous treatments with **GAMMAGARD S/D**, even though it contains low levels of IgA. If a hypersensitivity reaction occurs, discontinue infusion immediately and institute appropriate treatment. IgA-deficient patients with antibodies to IgA are at greater risk of developing potentially severe hypersensitivity reactions, including anaphylaxis.

Renal Dysfunction/Failure: Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur with IV use of IG products, especially those containing sucrose. Acute renal failure has been reported in association with **GAMMAGARD LIQUID** and **GAMMAGARD S/D**. Ensure patients are not volume depleted prior to infusion. In patients at risk due to pre-existing renal insufficiency or predisposition to acute renal failure, assess renal function before initiation and throughout treatment, and consider lower, more frequent dosing. If renal function deteriorates, consider discontinuation.

Thrombosis: Has been reported to occur following treatment with IG products, including **HYQVIA** and in the absence of known risk factors. In patients at risk, administer at the minimum dose and infusion rate practicable. Ensure adequate hydration before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Aseptic Meningitis Syndrome: Has been reported with use of IG, including **HYQVIA** and may occur more frequently in females. Conduct a thorough neurological exam on patients exhibiting signs and symptoms, to rule out other causes of meningitis. Discontinuing IG treatment has resulted in remission within several days without sequelae. The syndrome usually begins within several hours to two days following IG treatment.

Hemolysis: **CUVITRU**, **HYQVIA**, **GAMMAGARD LIQUID**, and **GAMMAGARD S/D** contain blood group antibodies, which may cause a positive direct antiglobulin reaction and hemolysis. Monitor patients for signs and symptoms of hemolysis and delayed hemolytic anemia and, if present, perform appropriate confirmatory lab testing.

Transfusion-Related Acute Lung Injury: Non-cardiogenic pulmonary edema may occur with IV administered IG. Monitor patients for pulmonary adverse reactions. If suspected, perform appropriate tests for presence of anti-neutrophil and anti-HLA antibodies in both product and patient serum. May be managed using oxygen therapy with adequate ventilatory support.

Transmittable Infectious Agents: Because **CUVITRU**, **HYQVIA**, **GAMMAGARD LIQUID**, and **GAMMAGARD S/D** are made from human plasma, they may carry a risk of transmitting infectious agents (e.g., viruses, other pathogens). No confirmed cases of viral transmission of variant Creutzfeldt-Jakob disease (vCJD) have been associated with **CUVITRU** or **GAMMAGARD LIQUID**, and no cases have been associated with **HYQVIA**.

Interference with Lab Tests: False positive serological test results and certain assay readings, with the potential for misleading interpretation, may occur as the result of passively transferred antibodies.

Additional Warnings and Precautions for HYQVIA

Immunogenicity of Recombinant Human Hyaluronidase (rHuPH20): Non-neutralizing antibodies to the Recombinant Human Hyaluronidase component can develop. The clinical significance of these antibodies or whether they interfere with fertilization in humans is unknown.

Spread of Localized Infection: Do not infuse **HYQVIA** into or around an infected area due to potential risk of spreading a localized infection.

Please see Full Indication and Important Safety Information on next page and click for Full Prescribing Information for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

IMPORTANT SAFETY INFORMATION (cont'd)

Additional Warnings and Precautions for GAMMAGARD LIQUID and GAMMAGARD S/D

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur. It is critical to distinguish true hyponatremia from a pseudohyponatremia because certain treatments may lead to volume depletion, a further increase in serum viscosity, and a predisposition to thromboembolic events.

Alterations in serum sodium levels (i.e., acute hypernatremia, pseudohyponatremia) may occur with **GAMMAGARD S/D**. In patients on a low sodium diet, calculate the amount of sodium from **GAMMAGARD S/D** when determining dietary sodium intake.

Adverse Reactions

CUVITRU

The most common adverse reactions observed in ≥5% of patients in clinical trials were local adverse reactions including mild or moderate pain, erythema, and pruritus, and systemic adverse reactions including headache, nausea, fatigue, diarrhea, and vomiting.

HYQVIA

The most common adverse reactions observed in >5% of patients in clinical trials were local adverse reactions including pain, erythema, edema, and pruritus, and systemic adverse reactions including headache, antibody formation against Recombinant Human Hyaluronidase (rHuPH20), fatigue, nausea, pyrexia, and vomiting.

GAMMAGARD LIQUID for PI

IV administration: The serious adverse reaction seen during IV clinical trials was aseptic meningitis. The most common adverse reactions observed in ≥5% of patients in clinical trials were headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur.

Subcutaneous administration: The most common adverse reactions observed in ≥5% of patients in clinical trials were infusion site (local) event (rash, erythema, edema, hemorrhage, and irritation), headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.

GAMMAGARD S/D

The most common adverse reactions observed in ≥5% of clinical trial patients during or within 48 hours of infusion were headache, nausea, chills, fatigue, pyrexia, upper abdominal pain, diarrhea, back pain, infusion site pain, hyperhidrosis, and flushing.

The most serious adverse reactions reported postmarketing include renal failure, thrombotic events (myocardial infarction, cerebrovascular accidents, and pulmonary embolism), anaphylactic shock, aseptic meningitis, and hemolysis.

Drug Interactions

Passive transfer of antibodies may transiently interfere with the immune responses to live attenuated virus vaccines (e.g., measles, mumps, rubella, and varicella).

Use In Specific Populations

Pregnancy: Limited human data are available on the use of **HYQVIA** during pregnancy. The effects of antibodies to the Recombinant Human Hyaluronidase on the human embryo or fetal development are unknown. It is not known whether **HYQVIA** can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. **HYQVIA** should be given to a pregnant woman only if clearly needed.

Please click for Full Prescribing Information, including Boxed Warnings regarding Thrombosis, Renal Dysfunction, and Acute Renal Failure, for CUVITRU, HYQVIA, GAMMAGARD LIQUID, and GAMMAGARD S/D.

References

1. CUVITRU [Prescribing Information]. Lexington, MA: Baxalta US Inc.
2. HYQVIA [Prescribing Information]. Lexington, MA: Baxalta US Inc.
3. GAMMAGARD LIQUID [Prescribing Information]. Westlake Village, CA: Baxalta US Inc.
4. GAMMAGARD S/D [Prescribing Information]. Westlake Village, CA: Baxalta US Inc.
5. Academy of Managed Care Pharmacy. Concepts in managed care pharmacy: prior authorization. amcp.org/prior_authorization/. Accessed April 25, 2023.
6. Medical Mutual. Immune globulin subcutaneous (SCIG) prior approval criteria. March 2018. https://provider.medmutual.com/PDF/RxMgmt/DrugClass/FINAL%20SCIG%20Drug%20Policy.pdf?t=1/22/2018%202:46:33%20AM. Accessed April 25, 2023.
7. CVS Caremark. Immune globulins subcutaneous and intravenous. https://www.caremark.com/portal/asset/HMSAFaxForm_ImmuneGlobulins.pdf. Accessed April 25, 2023.
8. Emblem Health. Intravenous immune globulins (immune globulin). https://www.emblemhealth.com/-/media/Files/PDF/_med_guidelines/MG_IVIG.pdf. Accessed April 25, 2023.
9. Aetna. Drug infusion site of care policy. https://www.aetna.com/health-care-professionals/utilization-management/drug-infusion-site-of-care-policy.html. Accessed April 25, 2023.
10. UnitedHealthcare. Provider administered drugs –site of care. https://www.uhcprovider.com/content/dam/provider/docs/public/policies/signaturevalue-mmg/provider-administered-drugs-site-care-review-guidelines-sv.pdf. Accessed April 25, 2023.
11. IG Living. How to write an effective appeal letter. www.igliving.com/assets/downloads/IGL-how-to-Write-an-Effective-Appeal-Letter.pdf. Accessed April 25, 2023.
12. IG Living. Transitioning IG coverage to Medicare. www.igliving.com/magazine/articles/IGL_2015-10_AR_Transitioning-IG-Coverage-to-Medicare.pdf#search=%22transition%20to%20medicare%22. Accessed April 25, 2023.
13. Immune Deficiency Foundation. Is IVIG or SCIG treatment covered under Medicare Part B or Part D? https://primaryimmune.org/faq/medical-insurance/ivig-or-scig-treatment-covered-under-medicare-part-b-or-part-d. Accessed April 25, 2023.
14. Medicare Benefit Policy Manual. Chapter 15: Covered Medical and Other Health Services. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf. Accessed April 25, 2023.
15. Centers for Medicare and Medicaid Services. ICD-10-CM Index to Diseases and Injuries. https://www.cms.gov/medicare/icd-10/2023-icd-10-cm. Accessed April 25, 2023.
16. Centers for Medicare and Medicaid Services. 2019 HCPCS Alpha-Numeric Index. https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Alpha-Numeric-HCPCS.html. Accessed April 25, 2023.
17. Centers for Medicare and Medicaid Services. Search the Physician Fee Schedule. https://www.cms.gov/medicare/physician-fee-schedule/search. Accessed April 25, 2023.

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