

Pharmacy Medical Necessity Guidelines: Immune Globulin (IVIg, SCIG)

Effective: April 20, 2020

Prior Authorization Required	√	Type of Review – Care Management	
Not Covered		Type of Review – Clinical Review	√
Pharmacy (RX) or Medical (MED) Benefit	MED /RX	Department to Review	PRECERT /MM
<p>These pharmacy medical necessity guidelines apply to the following:</p> <p>Commercial Products</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Tufts Health Plan Commercial products – large group plans <input checked="" type="checkbox"/> Tufts Health Plan Commercial products – small group and individual plans <input checked="" type="checkbox"/> Tufts Health Freedom Plan products – large group plans <input checked="" type="checkbox"/> Tufts Health Freedom Plan products – small group plans • CareLinkSM – Refer to CareLink Procedures, Services and Items Requiring Prior Authorization <p>Tufts Health Public Plans Products</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Tufts Health Direct – A Massachusetts Qualified Health Plan (QHP) (a commercial product) <input checked="" type="checkbox"/> Tufts Health Together – MassHealth MCO Plan and Accountable Care Partnership Plans <input checked="" type="checkbox"/> Tufts Health RITogether – A Rhode Island Medicaid Plan 		<p>Fax Numbers:</p> <p>Tufts Health Plan Commercial Plans and Tufts Health Freedom Plan products: PRECERT: 617.972.9409</p> <p>Tufts Health Public Plans: MM: 888.415.9055</p>	

Note: This guideline does not apply to Medicare Members (includes dual eligible Members).

OVERVIEW

FOOD AND DRUG ADMINISTRATION (FDA)-APPROVED INDICATIONS

Effective May 1, 2020, prior authorization for Tufts Health Plan Commercial Products, Tufts Health Direct, and Tufts Health RITogether Members <18 years of age is not required for any immune globulin product.

Effective October 1, 2019, prior authorization for Tufts Health Together Members <18 years of age is not required for any immune globulin product.

Specific FDA-approved uses vary for individual products. Currently available immune globulin intravenous [human] (IVIg) products may be labeled for the treatment of primary immunodeficiency diseases (PID), idiopathic thrombocytopenic purpura (ITP), Kawasaki disease (KD), B-cell chronic lymphocytic leukemia (CLL), chronic inflammatory demyelinating polyneuropathy (CIDP), and/or multifocal motor neuropathy (MMN). Immune globulin subcutaneous [human] (SCIG) products are currently labeled for the treatment of PID only.

See table below for FDA-approved indications of currently marketed products:

Brand Name	PID	ITP	KD	CLL	CIDP	MMN
Asceniv	X					
Bivigam	X					
Carimune® NF	X	X				
Cutaquig®	X					
Cuvitru®	X					
Flebogamma 5% DIF	X					
Flebogamma 10% DIF	X	X				
Gammagard Liquid*	X					X
Gammagard S/D	X	X	X	X		
Gammaked*	X	X			X	
Gammplex	X					
Gamunex®	X	X			X	
Gamunex®-C*	X	X			X	

Brand Name	PID	ITP	KD	CLL	CIDP	MMN
Hizentra®	X				X	
HyQvia	X					
Octagam®	X					
Panzyga®	X	X				
Privigen®	X	X			X	
Xembify®	X					

*Gammagard Liquid, Gammaked and Gamunex-C, when administered subcutaneously, are FDA-approved for the treatment of primary immunodeficiency syndromes *only*. Gammagard Liquid, Gammaked and Gamunex-C are not approved for subcutaneous use in patients with ITP or CIDP.

Immune globulin preparations are available as pre-mixed liquids or lyophilized powders with varying concentrations of IgG. The manufacture of commercial immune globulin products from pooled plasma is a complex multistep process consisting of fractionation, purification, stabilization, virus inactivation, and virus removal and as a result, immune globulin products differ with respect to formulation and composition. Product characteristics such as content (e.g., IgA concentration, stabilizer), volume, and osmolarity may be important considerations for some patients. However, comparative data are lacking and it is not known whether one specific product is superior for a particular disease or clinical setting.

At present, six immune globulin products are FDA-approved for subcutaneous administration in patients with PID. Compared with the intravenous route, the subcutaneous route may offer some advantages in terms of improved tolerability, better sustained blood levels of IgG, and ability to be self-administered at home. Clinical experience with subcutaneous administration of immune globulin for treating conditions other than PID is limited at this time and is generally not recommended.

Immune globulin is the standard treatment for PID. PID includes, but are not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Other FDA-approved indications for immune globulin include ITP, B-cell CLL, CIDP, and Kawasaki syndrome as outlined above. In addition, in clinical practice, immune globulin is frequently used for treating a variety of off-label conditions in various therapeutic areas such as neurology, hematology, infectious disease, stem cell transplant, dermatology, and rheumatology. However, many of these off-label or proposed uses lack quality evidence of clinical benefit. Given the increasing demand and limited supply of immune globulin, along with the potential risks and relatively high cost of therapy, the indications for use of immune globulin require careful consideration.

COVERAGE GUIDELINES

The plan may authorize coverage of Immune Globulin (see Limitations section for specific requirements for coverage of Hizentra®) when medically necessary and proven effective for Members with specific humoral immunodeficiencies or other clinical conditions as listed in the Pharmacy Coverage Guidelines below when the use of immune globulin, including but not limited to dosage, frequency, site of administration, and duration of therapy, is clinically appropriate and supported by evidence-based literature. Adjustments of dosage, frequency, site of administration, and duration of therapy must be reasonable and appropriate based on condition and severity, availability of alternative treatments, and prior response to immune globulin therapy.

The plan does not cover Intravenous Immune Globulin or Subcutaneous Immune Globulin for other medical conditions, diseases and disorders, including but not limited to conditions listed in the Limitations section of these Medical Necessity Guidelines, when its use is considered investigational or unproven, and is not supported by evidence-based literature.

Initial Authorization

The plan may authorize coverage of Intravenous Immune Globulin or Subcutaneous Immune Globulin (see Limitations section for specific requirements for coverage of Hizentra®) when **ALL** of the following criteria are met:

1. The medical diagnosis is listed as a covered medical condition below
AND
2. A definitive diagnosis of the covered medical condition has been made by a specialist and documented by clinical notes including appropriate positive findings on diagnostic testing and/or biopsy results

AND

3. The criteria specific for the covered medical condition below are met and documented by clinical notes and laboratory test results as required

AND

4. The requested frequency and dosage of Intravenous Immune Globulin or Subcutaneous Immune Globulin is supported by evidence-based literature (please submit complete documentation for requests outside the recommended dosing guidelines)

Note: Initial authorizations, including initial authorizations for ongoing treatment are limited to a maximum of 3 months.

Reauthorization

The plan may reauthorize coverage of Intravenous Immune Globulin or Subcutaneous Immune Globulin (see Limitations section for specific requirements for coverage of Hizentra®) when **ALL** of the following criteria are met:

1. The treated medical condition has not resolved

AND

2. Documentation of sustained clinical benefit of Immune Globulin treatment as evidenced by medical records documenting current progress and the expected frequency and duration of any additional Intravenous Immune Globulin or Subcutaneous Immune Globulin use going forward has been submitted. Objective monitoring of progress using metric assessment may be used. Examples are the Inflammatory Neuropathy Cause and Treatment (INCAT) scale, the Medical Research Council (MRC) scale, and activities of daily living (ADL) measurements

AND

3. The Immune Globulin treatment does not exceed any applicable duration of therapy limit detailed for the covered medical condition below

AND

4. The Member has been stabilized on or titrated to the minimum dosage and frequency to achieve sustained clinical effect where clinically appropriate

Note:

1. Subsequent reauthorization requests may be approved in up to 6-month intervals except for covered primary humoral immunodeficiencies which may be approved in up to 12-month intervals.
2. Depending on the diagnosis and clinical circumstances, an attempt should be made to decrease or wean the dosage when improvement has occurred. If improvement is sustained with dosage reduction, there should be, when clinically appropriate, an attempt to stop administration of Intravenous Immune Globulin or Subcutaneous Immune Globulin.
3. If improvement does not occur with Intravenous Immune Globulin or Subcutaneous Immune Globulin, continued administration may not be considered medically necessary.

Covered Medical Conditions & Clinical Coverage Criteria

Covered Medical Condition	Clinical Coverage Criteria
Dermatology	
Autoimmune mucocutaneous blistering diseases (AMBDS): Bullous pemphigoid; Epidermolysis Bullosa Acquisita (EBA); Mucous membrane pemphigoid (a.k.a. Cicatricial Pemphigoid); Pemphigus Foliaceus; Pemphigus Vulgaris	<ul style="list-style-type: none">• Biopsy-proven diagnosis of AMBDs (including pathology report) AND meets one of the following criteria:• Use only for short-term therapy, not as maintenance therapy, (see dosing recommendation for definition of treatment failure) <p style="text-align: center;">OR</p> <ul style="list-style-type: none">• Failure of conventional therapy—defined as failure of disease control after a maximum dose of 60 mg daily of prednisone (or prednisone 1 mg/kg/day) for 6 weeks, with, or without a concurrently administered ISA, e.g., Imuran 150 mg per day or Cytoxan 100 mg per day for a maximum of 10-to-12 weeks <p style="text-align: center;">OR</p> <ul style="list-style-type: none">• Significant adverse effects of conventional therapy -defined as adverse reactions that are potentially life-threatening, cause significant morbidity or inability to cope with activities

Covered Medical Condition	Clinical Coverage Criteria
	<p>of daily living, and require the intervention of a physician or drug therapy</p> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Contraindications to conventional therapy, for systemic corticosteroids (existing diabetes, clinically significant osteoporosis, fractures, upper GI bleeding, posterior subcapsular cataracts, pseudotumor cerebri, bone marrow suppression, aplastic anemia, clinically significant psychological changes, steroid myopathy, glaucoma); and for immunosuppressive agents (significant persistent anemia, clinically significant neutropenia, clinically significant abnormal hepatic function, clinically significant impaired renal function, hemorrhagic cystitis, clinically significant bone marrow suppression, history of malignancy) <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Patients with rapidly progressive disease which significantly impacts activities of daily living, in spite of appropriate maximum, yet safe conventional systemic therapy <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Patients with EBA with generalized cutaneous diseases with or without multiple mucosal involvement, that is rapid and progressive • Dosing recommendation: <ul style="list-style-type: none"> – Up to 2,000 mg/kg per course of therapy administered in divided doses over 3-to-5 days every 3-to-4 weeks, monthly for up to 6 months. <p>Reauthorization requests:</p> <ul style="list-style-type: none"> • For Members who require additional therapy following 6 months of maximum therapy, intervals between infusion cycles are gradually increased to 6, 8, 10, 12, 14, and 16 weeks. When a relapse occurs, the frequency of infusions would be temporarily increased to a 4-week interval until the clinical condition stabilizes and no new lesions are observed. Then the increase in intervals between infusions is resumed. The last two cycles are given at 16-week intervals. The second 16-week cycle is the end point of therapy at which the patient remains free of lesions. • Treatment failure at 6 months is defined as either no significant clinical response or inability to decrease the conventional therapy dose by at least 25%. • Additional therapy beyond 6 months will be evaluated for Members who did not fail treatment.
<p>Dermatomyositis/Polymyositis, including Juvenile</p>	<ul style="list-style-type: none"> • Biopsy-proven diagnosis • For the diagnosis of dermatomyositis, Member presents with skin lesions (i.e., heliotrope rash, Gottron’s sign, or erythema on the extensor surface of extremity joints) • For the diagnosis of both dermatomyositis and polymyositis the Member presents with at least four of the following: <ul style="list-style-type: none"> – Elevated serum CK (creatin kinase) or aldolase level – Muscle pain on grasping or spontaneous pain – Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials) – Non-destructive arthritis or arthralgias – Pathological findings compatible with inflammatory myositis – Positive anti-Jo-1 (histadyl tRNA synthetase) antibody

Covered Medical Condition	Clinical Coverage Criteria
	<ul style="list-style-type: none"> - Proximal muscle weakness (upper or lower extremity and trunk) - Systemic inflammatory signs (e.g., fever, elevated serum CRP level or accelerated ESR of more than 20 mm/h by the Westergren method) • Failure, contraindication or intolerance to both first and second-line therapies: <ul style="list-style-type: none"> - First-line: corticosteroids (e.g., prednisone) - Second-line: Immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, Rituxan®) - At least a 4-month trial of standard therapies is required unless there is profound, rapidly progressive and / or potentially life-threatening muscular weakness refractory to prior therapy. - Refractory disease is evidenced by persistently elevated serum creatine kinase and / or lack of improvement on muscle strength improvement scales. • Dosing recommendation: <ul style="list-style-type: none"> - Initial dose: 2,000 mg/kg divided over 3 to 5 days • Maintenance dose: 500 – 1,000 mg/kg per month.
Pyoderma gangrenosum	<ul style="list-style-type: none"> • Failure, contraindication or intolerance to at least two (2) systemic therapies: <ul style="list-style-type: none"> - Systemic corticosteroids - Immunosuppressants (e.g., azathioprine, mercaptopurine, mycophenolate mofetil, cyclosporine, cyclophosphamide, chlorambucil) - Dapsone - Infliximab (Remicade®) - For localized pyoderma gangrenosum intralesional injections of corticosteroids or cyclosporine.
Infectious Disease	
Acute disseminated encephalomyelitis	Failure, contraindication or intolerance to intravenous corticosteroid treatment.
Erythrovirus (formerly parvovirus) B19 Infection, chronic, with severe anemia (Pure Red Cell Aplasia)	Member has severe, refractory anemia with documented erythrovirus B19 viremia.
HIV and AIDS	<ul style="list-style-type: none"> • Age less than 13 years old • Entry CD4+ lymphocyte counts greater than or equal to 200/mm³ • Evidence of either qualitative or quantitative humoral immunologic defects • Recurrent bacterial infections, despite appropriate antimicrobial prophylaxis and effective antiretroviral therapy • Dosing recommendation: <ul style="list-style-type: none"> - 400 mg/kg given every 28 days
HIV-associated thrombocytopenia – Adults	<ul style="list-style-type: none"> • Platelet count is < 20,000/μL <li style="text-align: center;">OR • Thrombocytopenic Member with significant bleeding <li style="text-align: center;">OR • Failure of RhIG in Rh-positive patients

Covered Medical Condition	Clinical Coverage Criteria
HIV-associated thrombocytopenia – Pediatric	<ul style="list-style-type: none"> • Age less than 13 years of age • IgG level is less than 400 mg/dL and one of the following criteria is met: <ul style="list-style-type: none"> - Member has had at least two bacterial infections in a 1-year period despite appropriate antibiotic prophylaxis (e.g., TMP-SMZ) <p style="text-align: center;">OR</p> - Member has received two doses of measles vaccine and lives in a region with a high prevalence of measles <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> - Member has HIV-associated thrombocytopenia despite anti-retroviral therapy <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> - Member has chronic bronchiectasis and a suboptimal response to antimicrobial and pulmonary therapy <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> - T4 cell count is greater than or equal to 200/mm³.
Prevention of infection in HIV-infected children	<p>The plan covers immune globulin for prevention of infection in HIV-infected children consistent with the recommendations of the Working Group on Antiretroviral Therapy of the National Pediatric HIV Resource Center when one of the following criteria are met:</p> <ul style="list-style-type: none"> • Member has hypogammaglobulinemia (serum IgG concentration < 250 mg/dL) • Member has recurrent serious bacterial infections defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 1-year period • Member has failed to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine • Member is living in areas where measles is highly prevalent and Member has not developed an antibody response after two doses of measles, mumps, and rubella virus vaccine live • Single dose of immune globulin may be authorized for HIV-infected children who are exposed to measles • Member has chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy.
Immunology	
Primary Humoral Immunodeficiencies	
Common Variable Immunodeficiency (CVID)	<ul style="list-style-type: none"> • Evidence of qualitative and/or quantitative antibody production deficiency • IgG level must be below the normal range (>2 standard deviations below the age-specific mean) on at least two occasions while the Member is clear of infections • Laboratory results showing low IgA and IgM levels • Documented recurrent bacterial infections resulting from low IgG or serious bacterial infections • Failure of prophylactic antibiotic therapy • For reauthorization, immune globulin therapy must reduce the number and severity of clinical infections • Dosing Recommendation: <ul style="list-style-type: none"> - 100 to 500 mg/kg IV monthly.

Covered Medical Condition	Clinical Coverage Criteria
Congenital agammaglobulinemia (X-linked agammaglobulinemia)	<ul style="list-style-type: none"> • Evidence of qualitative and/or quantitative antibody production deficiency • IgA, IgG and IgM levels must be below the normal range (>2 standard deviations below the age-specific mean) on at least two occasions while the Member is clear of infections • Documented recurrent bacterial infections resulting from low IgG or serious bacterial infections • For reauthorization, immune globulin therapy must reduce the number and severity of clinical infections • IgG trough level should be measured prior to therapy, at 3 to 6 months and every 6 months thereafter • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV monthly.
Hypogammaglobulinemia (excluding IgA deficiency)	<ul style="list-style-type: none"> • Evidence of qualitative and/or quantitative antibody production deficiency • IgG level must be below the normal range (>2 standard deviations below the age-specific mean) on at least two occasions while the Member is clear of infections • History of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy or failure of prophylactic antibiotic therapy • Management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV monthly.
Selective IgG subclass deficiency	<ul style="list-style-type: none"> • Deficiency of one or more IgG subclasses below the normal range (>2 standard deviations below the age-specific mean) assessed on at least two occasions while the Member is free of infections • Unexplained recurrent or persistent severe bacterial infections despite appropriate treatment with all of the following: <ul style="list-style-type: none"> – Aggressive management of underlying conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis) – Prophylactic antibiotics – Increased vigilance and appropriate antibiotic therapy for infections – Immunization with conjugate vaccines in patients who have not responded to polysaccharide vaccines • Inadequate response to protein and polysaccharide antigens, as determined by the following: <ul style="list-style-type: none"> – Documented inability to mount an antibody response to protein antigens (Serum antibody titers to tetanus and / or diphtheria should be obtained prior to immunization with diphtheria and / or tetanus vaccine and 3 to 4 weeks after immunization. An inadequate response is defined as less than a 4-fold rise in antibody titer and lack of protective antibody level) – Documented inability to mount an adequate antibody response to polysaccharide antigens (Serum antibody titers to ≥14 pneumococcus serotypes should be measured prior to immunization and 3 to 6 weeks after immunization with polyvalent pneumococcal polysaccharide vaccine. An inadequate response is defined as less than a 4-fold rise in titer over baseline in at least

Covered Medical Condition	Clinical Coverage Criteria
	<p>30 % of serotypes tested (in at least 50 % of serotypes tested in children aged 2 to 5 years) and lack of protective antibody level [i.e., specific IgG concentration less than 1.3 mcg/ml])</p> <p>Reauthorization</p> <ul style="list-style-type: none"> • Immune globulin therapy must reduce the number and / or severity of infections. • Discontinue and reevaluate the medical necessity of immune globulin one year after initiating therapy and every two years thereafter by re-assessing immune response to protein and polysaccharide antigens. • Immune response should be re-evaluated at least 3 months after discontinuation of immune globulin.
Severe combined immunodeficiency (SCID)	<ul style="list-style-type: none"> • Evidence of qualitative and/or quantitative antibody production deficiency <ul style="list-style-type: none"> – Laboratory findings of low T cells, low IgA, IgE and IgM supporting the diagnosis • Documented recurrent or serious bacterial infections directly attributable to this deficiency • IgG trough level should be measured prior to therapy, at 3 to 6 months and every 6 months thereafter • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV monthly.
Specific antibody deficiency (SAD)	<ul style="list-style-type: none"> • Documented normal serum IgG, IgA, and IgM • Normal responses to protein antigens (tetanus and diphtheria toxoid or HiB) measured 3 – 4 weeks after immunization • Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by: <ul style="list-style-type: none"> – Age < 6 years, < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype) – Age ≥ 6 years, < 70% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype) • Inadequate responsiveness to pneumococcal conjugate vaccine (Prenar 13®) 4–8 weeks after vaccination as defined by: <ul style="list-style-type: none"> – Age < 6 years, < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype) – Age ≥ 6 years, < 70% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype) • Unexplained recurrent or persistent severe bacterial infections despite appropriate treatment with all of the following: <ul style="list-style-type: none"> – Aggressive management of underlying conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis) – Prophylactic antibiotics – Increased vigilance and appropriate antibiotic therapy for infections

Covered Medical Condition	Clinical Coverage Criteria
Wiskott-Aldrich Syndrome	<ul style="list-style-type: none"> • Confirmed diagnosis of Wiskott-Aldrich Syndrome • Evidence of qualitative and/or quantitative antibody production deficiency • IgG level must be below the normal range (>2 standard deviations below the age-specific mean) on at least two occasions while the Member is clear of infections • Documented recurrent or serious bacterial infections • For reauthorization, immune globulin therapy must reduce the number and severity of clinical infections • IgG trough level should be measured prior to therapy, at 3 to 6 months and every 6 months thereafter • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV monthly.
X-linked immunodeficiency with hyperimmunoglobulin M	<ul style="list-style-type: none"> • Evidence of qualitative and/or quantitative antibody production deficiency • IgG levels must be below the normal range (>2 standard deviations below the age-specific mean) on at least two occasions while the Member is clear of infections • Flow cytometry testing is supportive of diagnosis • Documented recurrent bacterial infections resulting from low IgG or serious bacterial or opportunistic infections • For reauthorization, immune globulin therapy must improve the number and severity of clinical infections • IgG trough level should be measured prior to therapy, at 3 to 6 months and every 6 months thereafter • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV monthly
Hematology / Oncology	
Autoimmune Hemolytic Anemia, warm-type	<ul style="list-style-type: none"> • Failure, contraindication or intolerance to both corticosteroids and splenectomy • Dosing Recommendation: <ul style="list-style-type: none"> – 1,000 mg/kg per day for 5 days
Bone Marrow Transplant / Stem Cell Transplant	<ul style="list-style-type: none"> • At risk for cytomegalovirus infection, pneumonia, or graft vs. host disease • Allogeneic or syngeneic transplant recipients requiring prophylaxis within the first 100 days post-transplant • Bone marrow transplant recipients with steroid-resistant graft-versus-host disease who are hypogammaglobulinemic (IgG level < 400 mg/dL) within the first 100 days post-transplant • After 100 days post-transplant: <ul style="list-style-type: none"> – Member is markedly hypogammaglobulinemic (IgG level < 400 mg/dL OR – Member has CMV, EBV or RSV infection • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV Monthly • Prophylaxis for cytomegalovirus should not exceed 90 days.

Covered Medical Condition	Clinical Coverage Criteria
Chronic Lymphocytic Leukemia (CLL) with hypogammaglobulinemia	<ul style="list-style-type: none"> • An immunoglobulin G (IgG) level of less than 600 mg/dl • Evidence of specific antibody deficiency <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Demonstrated recurrent bacterial infection <ul style="list-style-type: none"> – One severe bacterial infection within preceding 6 months or at least two bacterial infections in a 1-year period • Dosing Recommendation: <ul style="list-style-type: none"> – 100 to 500 mg/kg IV monthly
Fetal or neonatal alloimmune thrombocytopenia	<ul style="list-style-type: none"> • The Member has experienced a previous pregnancy affected by fetal alloimmune thrombocytopenia <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • A cordocentesis at 20 weeks reveals fetal platelets <100,000/μL <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • The neonate with severe thrombocytopenia is at high risk for developing intracranial hemorrhage when washed irradiated maternal platelets are not available, have not been successful, have become intolerable, or are contraindicated.
Idiopathic Thrombocytopenia Purpura (ITP) – Acute	<ul style="list-style-type: none"> • Management of acute bleeding due to severe thrombocytopenia (platelet counts less than 30,000/μl) • To increase platelet counts prior to invasive major surgical procedures (e.g., splenectomy); <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • In patients with severe thrombocytopenia (platelet counts less than 20,000/μL) considered to be at risk for intracerebral hemorrhage • Dosing recommendations: <ul style="list-style-type: none"> – 1,000 mg/kg body weight given on 1 or 2 consecutive days OR – 400 mg/kg body weight given on each of 2 to 5 consecutive days
Idiopathic Thrombocytopenia Purpura (ITP) – Chronic	<ul style="list-style-type: none"> • Prior treatment with corticosteroids and splenectomy • Duration of illness greater than 6 months • Age of 10 years or older • No concurrent illness/disease explaining thrombocytopenia, and • Platelet counts persistently at or below 20,000/μl • Dosing recommendations: <ul style="list-style-type: none"> – Initial – 1,000 or 2,000 mg/kg body weight (total cumulative dose) given in equal amounts over 2 to 5 days – Maintenance - 800 to 1,000 mg/kg body weight administered no more frequently than every 2 to 6 weeks as determined by serial platelet counts.
Multiple Myeloma or other immunoproliferative neoplasms	<ul style="list-style-type: none"> • Documented failure or inability to tolerate chemotherapy or radiation therapy. • IgG level less than 600 mg/dL • Evidence of specific antibody deficiency <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • "Plateau Phase" multiple myeloma (greater than 3 months since diagnosis) and at least two significant infections in last year or a single life threatening infection.
Neonatal autoimmune thrombocytopenia	<ul style="list-style-type: none"> • Platelet count is < 30,000/μL <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Member has bleeding complications related to thrombocytopenia

Covered Medical Condition	Clinical Coverage Criteria
Neonatal hemochromatosis, prophylaxis	<ul style="list-style-type: none"> Treatment of pregnant women with a history of pregnancy ending in documented neonatal hemochromatosis. Dosing Recommendation: <ul style="list-style-type: none"> – 1,000 mg/kg weekly from the 18th week until the end of gestation
Paraneoplastic opsoclonus-myoclonus-ataxia associated with neuroblastoma	Treatment of opsoclonus-myoclonus-ataxia associated with neuroblastoma.
Post-transfusion purpura	<ul style="list-style-type: none"> Platelet count less than 10,000/μL AND 2 to 14 days post-transfusion with bleeding complications Dosing Recommendation: <ul style="list-style-type: none"> – 400 – 500 mg/kg per day for 5 days OR – 1,000 mg/kg per day for 2 days – Typically single treatment
Secondary Hypogammaglobulinemia Due to: <ul style="list-style-type: none"> • Chemotherapeutic agents • Plasma Cell Leukemia (PCL) • Solid Organ Transplant 	<ul style="list-style-type: none"> IgG level below normal (>2 standard deviations below age-specific mean) on at least two occasions when the Member is clinically well Documented recurrent bacterial infections attributed to low IgG or serious bacterial / fungal infections OR Prophylaxis for Members with secondary hypogammaglobulinemia undergoing therapy that causes additional immunosuppression without demonstrated infections. For reauthorization requests <ul style="list-style-type: none"> • Documented reduction in the number and severity of clinical infections • For hypogammaglobulinemias expected to resolve over time, a trial off immune globulin must be considered. • Dosing Recommendation: <ul style="list-style-type: none"> – 300-500 mg/kg IV every 3-4 weeks
Toxic epidermal necrolysis/ Stevens–Johnson syndrome (TEN/SJS)	Acute treatment for severe cases only
Neurology	
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), also known as Chronic Relapsing Polyneuropathy, including diabetes mellitus-CIDP and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) variant	<ul style="list-style-type: none"> • Definitive diagnosis by a neurologist • Symmetric or focal neurologic deficits with slowly progressive or relapsing course over 2 months or longer with neurophysiological abnormalities • Nerve conduction study showing diffuse demyelination • Member is intolerant or refractory to therapeutic doses of corticosteroids OR for steroid sparing in the case of chronic steroid use • Dosing Recommendation: <ul style="list-style-type: none"> – Initial Therapy: 400 mg/kg per day for 5 days – Maintenance Therapy: 250-400 mg/kg no more frequently than every 2 weeks
Guillain-Barre Syndrome (acute) – Acute inflammatory demyelinating polyneuropathy (AIDP)	<ul style="list-style-type: none"> • The disorder has been diagnosed during the first 2 weeks of the illness • Immune globulin is initiated within one month of symptom onset. • Initial requests for therapy may be approved for two courses of therapy

Covered Medical Condition	Clinical Coverage Criteria
a.k.a. acute infective polyneuritis (includes GBS variants: Miller-Fisher syndrome, pan autonomic polyneuropathy, acute pandysautonomia, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy)	<ul style="list-style-type: none"> • Documented functional disability: <ul style="list-style-type: none"> – Significant weakness such as inability to stand or walk without aid, respiratory or bulbar weakness, or Miller-Fisher syndrome (MFS) • Plasmapheresis is not used concomitantly • Dosing Recommendation: <ul style="list-style-type: none"> – 400mg/kg per day for 5 days
Guillain-Barre Syndrome (chronic) – Chronic inflammatory demyelinating polyneuropathy (CIDP)	<ul style="list-style-type: none"> • Diffuse demyelination on nerve conduction study • Progressive symptoms have been present for ≥ 2 months • Symptomatic polyradiculoneuropathy as exhibited by both of the following: <ul style="list-style-type: none"> – Progressive or relapsing motor or sensory impairment of more than one limb – Widespread hyporeflexia or areflexia • Failure, contraindication or intolerance to therapeutic doses of corticosteroids • Dosing recommendation: <ul style="list-style-type: none"> – Maintenance Therapy; 400 to 1,000 mg/kg every 3 weeks
Lambert - Eaton Myasthenic Syndrome (LEMS)	<ul style="list-style-type: none"> • Treatment is initiated during or after treatment of the underlying malignancy if applicable • Previous treatment with one agent from any of the following therapeutic classes, or contraindication or clinical inappropriateness to all of the following therapeutic classes: <ul style="list-style-type: none"> – Acetylcholinesterase inhibitors (e.g., pyridostigmine) – Aminopyridines (e.g., Firdapse; Ampyra; 3,4-DAP) – Guanidine • Immune globulin is used as an alternative to plasma exchange if weakness is severe or when there is difficulty with venous access for plasmapheresis.
Multifocal motor neuropathy	<ul style="list-style-type: none"> • The Member must have a definitive diagnosis of progressive, symptomatic multifocal motor neuropathy by a neurologist. • Progressive symptoms present for at least 2 months. • Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in two or more nerves • No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs • Definite conduction block on one nerve or probable conduction block on two nerves • Normal sensory nerve conduction in upper limb segments with CB and normal sensory nerve action potential (SNAP) amplitudes • Dosing recommendation: <ul style="list-style-type: none"> – Initial therapy: 2,000 mg/kg IV divided over 2-5 days. – Maintenance therapy: up to 2,000 mg/kg every 3-4 weeks, then adjusted to maintain clinical response, typically 500 -1,000 mg/kg every 3-4 weeks.

Covered Medical Condition	Clinical Coverage Criteria
Myasthenia Gravis	Severe myasthenia gravis exacerbation: <ul style="list-style-type: none"> Acute myasthenic crisis with respiratory failure or impending respiratory failure with severe bulbar symptoms, when there is contraindication to plasmapheresis <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> Failure, contraindication or intolerance to other treatments (e.g., azathioprine, cyclosporine, and cyclophosphamide) Dosing recommendation: <ul style="list-style-type: none"> Single treatment: 2,000 mg/kg IV divided over 2-5 days
Relapsing/Remitting Multiple Sclerosis	<ul style="list-style-type: none"> The Member must have a definitive diagnosis of relapsing, remitting multiple sclerosis Immune globulin therapy must be prescribed by a neurologist The Member has a documented inadequate response to an appropriate trial with at least two of the following agents: Avonex® (interferon β-1a), Betaseron® or Extavia® (interferon β-1b), Plegridy® (interferon β-1a), Rebif® (interferon β-1a), Copaxone® (glatiramer acetate), Aubagio® (teriflunomide), Gilenya® (fingolimod), Tecfidera® (dimethyl fumarate), Lemtrada® (alemtuzumab), Tysabri® (natalizumab) or Zinbryta™ (daclizumab).
Stiff person syndrome, autoimmune, idiopathic, paraneoplastic (Moersch-Woltmann Syndrome)	<ul style="list-style-type: none"> Presence of anti-glutamic acid decarboxylase (anti-GAD) antibodies or anti-amphiphysin antibodies Failure, contraindication or intolerance to standard medical therapy <ul style="list-style-type: none"> baclofen Benzodiazepines (e.g., diazepam) clonidine Corticosteroids phenytoin Skeletal muscle relaxants (e.g., baclofen, tizanidine) Dosing recommendation: <ul style="list-style-type: none"> 2,000 mg/kg over 2-5 days no more frequently than every 6 weeks
Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS)	<ul style="list-style-type: none"> Documented diagnosis of PANDAS made by or in consultation with a pediatric psychiatrist or pediatric neurologist <p>Note: Coverage of Intravenous Immunoglobulin therapy for the treatment of PANDAS is limited to Tufts Health Freedom plans only, effective upon employer group renewal after 9/17/19 (see Limitations)</p>
Rheumatology	
Kawasaki Disease/Acute febrile mucocutaneous lymph node syndrome	<ul style="list-style-type: none"> Fever present for at least 5 days Treatment is initiated within ten days of onset of fever. Four of the following five symptoms are present: <ul style="list-style-type: none"> Mucous membrane changes such as a red tongue and dry fissured lips Swelling of the hands and feet Enlarged lymph nodes in the neck Diffuse red rash covering most of the body Redness of the eyes Oral aspirin is used concurrently as follows: oral aspirin 100 mg/kg daily until the 14th day of illness, then 3-5 mg/kg for a period of five weeks. Dosing Recommendation: <ul style="list-style-type: none"> 400mg/kg IV for 4 days or 1-2 grams/kg as a single dose

Covered Medical Condition	Clinical Coverage Criteria
Transplant	
Solid organ transplant	<p>Prior to transplant / peri-transplant:</p> <ul style="list-style-type: none"> • Immune globulin may be approved to reduce anti-HLA antibodies • Member is at high risk of antibody-mediated rejection <ul style="list-style-type: none"> – highly sensitized transplant recipients – ABO-incompatible organ transplant recipients <p>Post transplant</p> <ul style="list-style-type: none"> • Member experiences an antibody-mediated rejection <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • For treatment of CMV pneumonitis in combination with antiviral therapy <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • High risk Member for prevention of cytomegalovirus infection or pneumonia in combination with antiviral treatment <ul style="list-style-type: none"> – Prophylaxis for cytomegalovirus should not exceed 100 days post-transplant <p>Note: For secondary hypogammaglobulinemia due to solid organ transplant, see applicable criteria above.</p>
Other	
Birdshot (vitiliginous) retinochoroidopathy	Condition is not responsive to or Member has a contraindication to immunosuppressants (e.g., corticosteroids, cyclosporine)

LIMITATIONS

- The plan does not cover the subcutaneous immune globulin, Hizentra® unless the Member is unable to tolerate intravenous immune globulin or requires subcutaneous administration of immune globulin. Coverage criteria for intravenous immune globulin apply.
- For requests on behalf of Tufts Health Freedom Members with a diagnosis of PANDAS, authorizations will be granted for 12 months, with a quantity of two infusions. Requests for additional infusions within a 12 month period will be reviewed on an individual basis for medical necessity.
- For all other requests, initial authorizations for ongoing treatment are limited to maximum of 3 months. Subsequent reauthorization requests may be approved in up to 6 month intervals except for covered primary humoral immunodeficiencies which may be approved in up to 12 month intervals
- As there is inadequate evidence of efficacy and/or safety of treatment with IVIg or SCIG for the following conditions, the plan considers these uses experimental / investigational and will not approve coverage of IVIg and SCIG for any of the following conditions including but not limited to:

Hematologic / Oncologic Conditions

- Acquired factor VIII inhibitors
- Acute lymphoblastic leukemia
- Acute myelogenous leukemia
- Aplastic anemia
- Diamond-Blackfan anemia
- Hemophagocytic syndrome
- Non-immune thrombocytopenia
- Red cell aplasia
- Thrombotic thrombocytopenic purpura

Immunological Conditions

- Cellular immunodeficiencies
- Complement deficiencies
- Selective IgA deficiency

Infectious Conditions

- Chronic mucocutaneous candidiasis (CMCC)
- Chronic sinusitis

- Lyme disease
- Post-infectious sequelae
- Recurrent otitis media
- Rheumatic fever

Neurologic Conditions

- Alzheimer’s Disease
- Amyotrophic lateral sclerosis (ALS)
- Demyelinating optic neuritis
- Encephalopathy
- Epilepsy
- Multiple Sclerosis: primary progressive, secondary progressive, or progressive relapsing
- Parkinson’s Disease
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (Covered for Tufts Health Freedom plans members only when coverage criteria is met)
- Paraneoplastic syndromes other than Lambert-Eaton syndrome or paraneoplastic opsoclonus-myoclonus-ataxia associated with neuroblastoma
- Transverse myelopathy / myelitis

Rheumatologic Diseases

- Behçet’s syndrome
- Inclusion body myositis
- Reiter’s syndrome
- Rheumatoid arthritis
- Scleroderma
- Systemic Lupus Erythematosus
- Other vasculitides besides Kawasaki disease; including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA), Wegener’s granulomatosis, polyarteritis nodosa, Goodpasture’s syndrome, and vasculitis associated with other connective tissue diseases

Other Conditions

- Adrenoleukodystrophy
- Antiphospholipid syndrome
- Asthma
- Atopic dermatitis
- Chronic fatigue syndrome
- Cystic fibrosis
- Diabetes Mellitus
- Eczema
- Hemolytic uremic syndrome
- Henoch-Schönlein purpura (HSP)
- Idiopathic environmental illness
- Idiopathic lumbosacral flexopathy
- Idiopathic pulmonary fibrosis
- Organ transplant rejection
- Recent-onset dilated cardiomyopathy
- Recurrent fetal loss
- SICCA syndrome / Sjögren’s syndrome
- Uveitis (except Birdshot [vitiligenous] retinochoroidopathy)

CODES

The following HCPCS/CPT code(s) are:

Code	Description
90283	Immune Globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg

Code	Description
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (HyQvia), 100 mg immune globulin
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg
J1558	Injection, immune globulin (xembify), 100 mg

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APPROVAL HISTORY

January 2000: Reviewed by Pharmacy & Therapeutics Committee.

Subsequent endorsement date(s) and changes made:

1. July 12, 2005: No changes
2. June 13, 2006: Added Common Variable Immunodeficiency to letter b. of primary immunodeficiency criteria under Immunologic Conditions. Added criteria #6, "Relapsing / Remitting Multiple Sclerosis" under neurological conditions. Added agranulocytosis to criteria #2 under Immunologic conditions. Added criteria #5 (Plasma Cell Leukemia) and criteria #6 (Fetal Alloimmune Thrombocytopenia) under Oncology and Hematology. Added Limitation to section II, "The plan will not approve coverage of IVIg for progressive multiple sclerosis."
3. December 12, 2006: Added "Evidence of qualitative and/or quantitative antibody production deficiency" to the criteria for Common Variable Immunodeficiency, Hypogammaglobulinemia

- (excluding IgA deficiency) under Primary Humoral Immunodeficiency. Added Limitation #2: "The plan does not cover the subcutaneous immune globulin, Vivaglobin®."
4. March 13, 2007: Changed Limitation #2: The plan does not cover the subcutaneous immune globulin, Vivaglobin®, unless the Member is unable to tolerate intravenous immune globulin or requires subcutaneous administration of immune globulin.
 5. March 4, 2008: Added multifocal motor neuropathy as an approved diagnosis under the heading of, "Neurological Conditions."
 6. March 10, 2009: No changes
 7. January 1, 2010: Removal of Tufts Medicare Preferred language (separate criteria have been created specifically for Tufts Medicare Preferred).
 8. March 9, 2010: Administrative Update: Added medical billing code J1459
 9. July 13, 2010: Added Hizentra to limitation #2: The plan does not cover the subcutaneous immune globulins, Vivaglobin® and Hizentra® unless the Member is unable to tolerate intravenous immune globulin or requires subcutaneous administration of immune globulin. Removed criteria of (1) being intolerant or refractory to therapeutic doses of steroids or azathioprine and (2) neurologic function assessment score of at least three or greater on the Rankin Scale from coverage criteria for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
 10. January 1, 2011: Administrative Update: Added reimbursement codes C9270, J1559 and J1599
 11. July 12, 2011: Removed Vivaglobin from Medical Necessity Guidelines, product has been discontinued
 12. January 1, 2012: Administrative Update: Replaced reimbursement code C9270 with J1557. Added CPT codes 90281, 90283 and 90284.
 13. May 8, 2012: Changed MNG title from "Intravenous Immune Globulin (IVIg)" to "Immune Globulin (IVIG, SCIG)
 14. April 1, 2013: Administrative Update: Added reimbursement code C9130
 15. July 9, 2013 (updates will be effective on October 1, 2013): Administrative update: removed CPT code 90281; added coverage criteria for initial and reauthorization requests; added noncovered Hematologic / Oncologic, Immunologic, Infectious, Neurologic, Rheumatoid and other conditions indications to limitations; updated covered medical conditions and clinical coverage criteria.
 16. January 1, 2014: Administrative Update: Replaced reimbursement code C9130 with J1556.
 17. July 8, 2014: No changes
 18. July 14, 2015: Added HyQvia to Medical Necessity Guidelines.
 19. January 1, 2016: Administrative Update: Added reimbursement code J1575. Changed to rebranded template.
 20. July 12, 2016: Added Lemtrada, Plegridy and Zinbryta as prerequisite options for the diagnosis of relapsing, remitting multiple sclerosis.
 21. April 11, 2017: Administrative update. Effective 6/1/2017, Medical Necessity Guideline applies to Tufts Health RITogether.
 22. September 12, 2017: No changes
 23. January 1, 2018: Administrative update: Added new J code J1555 to Medical Necessity Guideline.
 24. April 10, 2018: Administrative update to the FDA-approved indications table in the Overview section to indicate that Privigen (IV) and Hizentra (SC) are approved for the treatment of chronic inflammatory demyelinating polyneuropathy.
 25. February 12, 2019: Clarified in the limitation section that coverage will not be granted for the treatment of uveitis, except Birdshot (vitiliginous) retinochoroidopathy.
 26. May 7, 2019: Updated therapeutic categories for symptomatic therapies for treatment of LEMS to include acetylcholinesterase inhibitors, aminopyridines, and guanidine.
 27. September 10, 2019: Added coverage of PANDAS for Tufts Health Freedom plans. Added note that effective October 1, 2019, prior authorization for Tufts Health Together Members <18 years of age is not required for any immune globulin product.
 28. October 15, 2019: Added Cutaquig and Panzyga to the Medical Necessity Guideline.
 29. November 12, 2019: Added Xembify to the Medical Necessity Guideline.
 30. April 12, 2020: Added note that effective May 1, 2020, prior authorization for Tufts Health Plan Commercial, Tufts Health Direct, and Tufts Health RITogether Members <18 years of age is not required for any immune globulin product. Added Asceniv to the Medical Necessity Guideline.

BACKGROUND, PRODUCT AND DISCLAIMER INFORMATION

Pharmacy Medical Necessity Guidelines have been developed for determining coverage for plan benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. The plan makes coverage decisions on a case-by-case basis considering the individual member's health care needs. Pharmacy Medical Necessity Guidelines are developed for selected therapeutic classes

or drugs found to be safe, but proven to be effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. The plan revises and updates Pharmacy Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

For self-insured plans, coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a Pharmacy Medical Necessity Guideline and a self-insured Member's benefit document, the provisions of the benefit document will govern.

Treating providers are solely responsible for the medical advice and treatment of members. The use of this policy is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to member eligibility and benefits on the date of service, coordination of benefits, referral/authorization and utilization management guidelines when applicable, and adherence to plan policies and procedures and claims editing logic.

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