



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Immune Globulin Intravenous (Human) (IGIV): Carimune™ NF, Flebogamma®, Gammagard™, Gammar®, P.I.V., Gamunex®, Iveegam® EN, Octagam®, Panglobulin® NF, Polygam® S/D

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Hyperlink to Related Coverage Policies

Immune Globulin Subcutaneous [Human] (Vivaglobin®)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

Coverage Policy

CIGNA covers intravenous immune globulin (human) (IVIG) as medically necessary for any of the conditions listed below when ALL of the following are present:

- The medical condition-specific criteria as listed below are fully met.
- The dosage, frequency, site of administration, and duration of therapy are reasonable clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to IVIG therapy for the condition begin addressed.

Initial authorizations are restricted to 3 months unless otherwise specified within the individual criteria listed below by indication.

A reauthorization for up to 6 months is covered as medically necessary when ALL of the following criteria are met:

- the medical condition or disease under treatment has not fully resolved and the treatment has not exceeded any applicable duration listed below.

- there continues to be a sustained beneficial response to Intravenous Immunoglobulin as evidenced by treatment notes or a clinical narrative detailing progress to date and the expected frequency and duration of any proposed IVIG use going forward.
- the requested frequency and dosage of Intravenous immunoglobulin is supported by evidence-based literature
- where clinically appropriate, titration has occurred to the minimum dose and frequency to achieve sustained clinical effect

Primary Immunodeficiency

Condition	Criteria for Use
<ul style="list-style-type: none"> ❖ Congenital / X-linked agammaglobulinemia-XLA <ul style="list-style-type: none"> ➢ Bruton’s Disease- BTK gene impaired ❖ Autosomal recessive agammaglobulinemia - ARA <ul style="list-style-type: none"> ➢ IGHM, CD79a, CD199b, BLNK, or LRRC8 gene impaired ❖ Autosomal recessive hyperimmuno-globulin M syndrome (HIM) <ul style="list-style-type: none"> ➢ AICDA or UNG gene impaired ❖ Congenital Hypogammaglobulinemia <ul style="list-style-type: none"> ➢ late onset, ICOS impaired ❖ ICF Syndrome <ul style="list-style-type: none"> ➢ Abnormal Facies ➢ Respiratory Track Infections ➢ Hypogammaglobulinemia ➢ Characteristic Chromosomal Abnormalities ❖ Specific Antibody Deficiency (SAD) <ul style="list-style-type: none"> ➢ generally does not require IVIG replacement for control of recurrent bacterial infections ➢ Rare patients will have infection susceptibility with normal vaccine responses ❖ Hypogammaglobulinemia, unspecified ❖ Transient hypogammaglobulinemia of infancy <ul style="list-style-type: none"> ➢ only requires short-term IVIG 	<p><u>One of the deficiency criteria (1,2,or 3 or 4) is required for coverage of a Primary Immunodeficiency</u></p> <p>1) <u>Agammaglobulinemia – any of the following:</u></p> <ul style="list-style-type: none"> ▪ Agammaglobulinemia defined as IgG<200 mg/dl ▪ Extremely low (<2%)or absent B cell count (CD19⁺) ▪ Genetic mutation consistent with a primary immunodeficiency <p>2) <u>Hypogammaglobulinemia with impaired specific antibody production as manifested by ALL of the following:</u></p> <ul style="list-style-type: none"> ▪ Hypogammaglobulinemia <ul style="list-style-type: none"> • IgG < 400mg /dl on at least 2 occasions • For CVID, IgG levels reduced to 2 standard deviations below the mean for age ▪ Impaired Antibody Response <ul style="list-style-type: none"> • <u>Lack of protective antibody titres (Tetanus and diphtheria or HiB) measured 3-4 weeks after immunization</u> • <u>Inadequate response to polysaccharide vaccine (pneumococcal vaccine) in at least 30% of the serotypes tested as evidenced by either a post immunization antibody concentration of 1.3 mcg/mL or less OR less than a 4-fold increase over baseline.</u> ▪ Recurrent Infection <ul style="list-style-type: none"> • history of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy • where applicable, evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections

Condition	Criteria for Use
<p>replacement for recurrent severe bacterial infections</p> <ul style="list-style-type: none"> ❖ Selective IgG subclass deficiencies (IGGSD) <ul style="list-style-type: none"> ➢ persistent absence of IgG1, IgG2, and/or IgG3 ➢ generally does not require IVIG replacement for control of recurrent bacterial infections ➢ Rare patients will have infection susceptibility with normal vaccine responses ❖ Combined immunodeficiency disorders (not all-inclusive) <ul style="list-style-type: none"> ➢ ataxia-telangiectasia (A-T) ➢ Wiskott Aldrich syndrome (WAS), ➢ DiGeorge syndrome (DGS) ➢ Nijmegen breakage syndrome (NBS) ➢ (WHIM) warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis ❖ Common variable immunodeficiency (CVID) ❖ Severe combined immunodeficiency disorder (SCID) ❖ Hyperimmuno-globulinemia E syndrome (HIES) 	<ul style="list-style-type: none"> • where applicable, supporting diagnostic imaging and/or laboratory results <p>3) <u>Normogammaglobulinemia with impaired specific antibody production as manifested by ALL of the following:</u></p> <ul style="list-style-type: none"> ▪ Immunglobulin Evaluation – one of the following <ul style="list-style-type: none"> ▪ For IgG sub-class deficiency, at least one IgG subclass deficiency as defined as 2 standard deviations below the age-adjusted mean ▪ For selective IgA deficiency, Serum IgA less than 0.07 g/L with normal IgG, IgM in an individual <u>older than 4 years.</u> ▪ <u>For Specific Antibody Deficiency (SAD), normal immunoglobulin levels</u> ▪ Impaired Antibody Response <ul style="list-style-type: none"> • <u>Lack of protective antibody titres (Tetanus and diphtheria or HiB) measured 3-4 weeks after immunization</u> • <u>Inadequate response to polysaccharide vaccine (pneumococcal vaccine) in at least 30% of the serotypes tested as evidenced by either a post immunization antibody concentration of 1.3 mcg/mL or less OR less than a 4-fold increase over baseline.</u> ▪ Recurrent Infection – either of the following <ul style="list-style-type: none"> • history of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy <ul style="list-style-type: none"> • where applicable, evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections • where applicable, supporting diagnostic imaging and/or laboratory results • for selective IgA deficiency, evidence of recurrent gastrointestinal infections <p>4) <u>ANY of the following</u></p> <ul style="list-style-type: none"> ▪ transient hypogammaglobulinemia of infancy with serum immunoglobulins below

Condition	Criteria for Use
	<p>the age-specific normal range and evidence of recurrent bacterial sinopulmonary infections requiring antibiotic therapy (IVIg is only used for up to 6 months before re-evaluating the need for continued treatment).</p> <ul style="list-style-type: none"> ▪ diagnosis of a combined immunodeficiency disorder with supporting documentation of a recognized genetic defect ▪ Hyperimmunoglobulinemia E syndrome as evidenced by an elevated serum IgE level, the presence of staphylococcus-binding IgE, eosinophilia, and recurrent lung and skin infections (abscess)

Secondary Immunodeficiency

Condition	Criteria for Use
High-risk, preterm, low-birth-weight neonates	Prevention or adjunct treatment for infection
Multiple Myeloma	Treatment when ALL of the following criteria are met: <ul style="list-style-type: none"> • disease is stable (> 3 months since diagnosis) • serum IgG < 600 mg/dL • recurrent bacterial sinopulmonary infections
B-cell chronic lymphocytic leukemia (CLL)	prevention of recurrent bacterial sinopulmonary infections in individuals with hypogammaglobulinemia secondary to CLL
Allogeneic hematopoietic stem cell transplant (HSCT)	Prevention of infection in allogeneic HSCT recipients with severe hypogammaglobulinemia for either of the following: <ul style="list-style-type: none"> • within the first 100 days after transplant for hypogammaglobulinemia • after 100 days for severe hypogammaglobulinemia (i.e., Immunoglobulin G [IgG] less than 400 mg/dL) and evidence of recurrent sinopulmonary infections
Allosensitized solid organ transplants	Treatment
Bone marrow transplantation (BMT)	Prevention of infection during the first 100 days following transplantation in BMT recipients age 20 years or older
HIV-infected children	Prevention of bacterial infections for CD4+ counts > 200/ μ L, when used in conjunction with antiretroviral treatment

Hematology

Condition	Criteria for Use
Acute idiopathic thrombocytopenic purpura (ITP)	Treatment for either of the following: <ul style="list-style-type: none"> • Active bleeding AND a platelet count < 30,000/mm³ • preoperative treatment prior to a major surgical procedure (e.g., splenectomy)
Chronic idiopathic thrombocytopenic purpura (ITP)	Treatment when all of the following are met: <ul style="list-style-type: none"> • Duration greater than 6 months. • No other concurrent illness/disease explaining thrombocytopenia • Prior treatment with a reasonable course of corticosteroids or splenectomy • Platelet count < 30,000/mm³ in children, or < 20,000/mm³ in adults

Condition	Criteria for Use
HIV-associated thrombocytopenia	Treatment for either of the following: <ul style="list-style-type: none"> Active bleeding AND a platelet count < 30,000/mm³ Platelet count <20,000/ mm³ preoperative treatment prior to a major surgical procedure (e.g., splenectomy)
Fetal alloimmune thrombocytopenia (FAIT)	Treatment for ALL of the following: <ul style="list-style-type: none"> Documentation of maternal antibodies to paternal platelet antigen Previous pregnancy complicated by FAIT Fetal blood sampling documents thrombocytopenia
Idiopathic thrombocytopenic purpura (ITP) in pregnancy	Treatment for ANY of the following: <ul style="list-style-type: none"> previously delivered infant(s) with autoimmune thrombocytopenia platelet count < 75,000/mm³ during the current pregnancy platelet count < 30,000/mL associated with bleeding before vaginal delivery or C-section refractory to corticosteroids - platelet counts < 10,000/mL in the third trimester history of splenectomy
Post-transfusion purpura	Acute treatment only
Neonatal isoimmune hemolytic disease in conjunction with phototherapy	Acute treatment only
Warm type autoimmune hemolytic anemia (characterized by predominance of IgG antibodies as opposed to cold type that is predominated by IgM antibodies)	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (i.e., azathioprine, cyclophosphamide, cyclosporine, prednisone, plasmapheresis, or splenectomy)
Anemia related to chronic parvovirus B19 infection	Treatment when there is a severe refractory anemia and evidence of viremia
Evan's syndrome	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (i.e., azathioprine, cyclophosphamide, cyclosporine or prednisone)

Neurology

Condition	Criteria for Use
Acute inflammatory demyelinating polyneuropathy (AIDP)	Acute treatment only
Myasthenia gravis	Treatment when ANY of the following is present <ul style="list-style-type: none"> before planned thymectomy or during the postoperative period following thymectomy during an acute crisis (e.g., significant dysphagia, respiratory failure, inability to perform physical activity) duration of treatment should not exceed 5 days during initiation of immunosuppressive treatment
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Treatment when ALL of the following are present: <ul style="list-style-type: none"> Progressive symptoms present for at least 2 months. Physical findings - symptomatic polyradiculoneuropathy

Condition	Criteria for Use
	<p>as indicated by BOTH of the following:</p> <ul style="list-style-type: none"> ○ progressive or relapsing motor or sensory impairment of more than one limb ○ widespread hyporeflexia or areflexia <p>i. Electrophysiologic Findings* (see American Academy of Neurology (AAN) conduction criteria note below): when Any 3 of the following 4 criteria are present:</p> <ul style="list-style-type: none"> • Partial conduction block of ≥ 1 motor nerve, • reduced conduction velocity of ≥ 2 motor nerves, • prolonged distal latency of ≥ 2 motor nerves, or • prolonged F-wave latencies of ≥ 2 motor nerves or the absence of F waves <ul style="list-style-type: none"> • CSF – both of the following findings following lumbar puncture <ul style="list-style-type: none"> • White blood cell count $< 10/mm^3$, • negative VDRL • For reauthorizations, significant improvement in clinical condition has been documented by an objective measurement such as Rankin, Modified Rankin, or MRC scales AND, when applicable, a reduction in the level of sensory loss should be noted. • For long-term treatment, evidence that the dose has been periodically reduced or the treatment withdrawn, and the effects measured.
<p>Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) (Lewis Sumner Syndrome)</p>	<p>Treatment when ALL of the following are present:</p> <ul style="list-style-type: none"> • Progressive symptoms present for at least 2 months. i. Physical findings - asymmetric presentations (multifocal acquired demyelinating sensory and motor [MADSAM] Lewis–Sumner syndrome Focal presentations (e.g. involvement of the brachial plexus or of one or more peripheral nerves in one upper limb) ii. Electrophysiologic Findings that show evidence of demyelinating neuropathy (such as partial conduction block, slow conduction velocities, temporal dispersion, prolonged distal and F wave latencies)
<p>Multifocal Motor Neuropathy (MMN)</p>	<p>Treatment when ALL of the following are present:</p> <ul style="list-style-type: none"> • Progressive symptoms present for at least 2 months. • Physical findings - as indicated by BOTH of the following: <ul style="list-style-type: none"> ○ Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves ○ No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs • Electrophysiologic Findings** (see Consensus Criteria For The Diagnosis Of Multifocal Motor Neuropathy from the American Association of Electrodiagnostic Medicine below): <ul style="list-style-type: none"> • Definite conduction block on 1 nerve or probable conduction block on 2 nerves,

Condition	Criteria for Use
	<ul style="list-style-type: none"> Normal sensory nerve conduction in upper limb segments with CB and normal sensory nerve action potential (SNAP) amplitudes
Relapsing-Remitting Multiple Sclerosis	Chronic treatment when there is failure, contraindication, or intolerance to standard conventional therapies (e.g. interferon beta, glatiramer).
Guillain-Barré syndrome (GBS)	Acute treatment when ALL of the following criteria have been met: <ul style="list-style-type: none"> initial treatment within 4 weeks of the onset of symptoms no concomitant use of plasmapheresis treatment may be repeated once but should not extend beyond 8 weeks from the onset of symptoms
Lambert-Eaton myasthenic syndrome (LEMS)	Treatment when there is failure, contraindication, or intolerance to other symptomatic therapies (e.g., acetylcholinesterase inhibitors such as mestinon and immunosuppressants such as prednisone, azathioprine)
Stiff person syndrome (Moersch-Woltmann Syndrome)	Treatment when there is failure, contraindication, or intolerance to available standard medical therapy (e.g. diazepam, baclofen, phenytoin, clonidine, or tizanidine)

*** American Academy of Neurology (AAN) criteria:**

- **A partial conduction block** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of < 15% in duration between proximal and distal site stimulation.
- **A possible conduction block or temporal dispersion** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of at least 15% in duration between proximal and distal site stimulation.
- **A reduced conduction velocity** is a velocity of < 80% of the lower limit of the normal range if the amplitude of the compound muscle action potential (CMAP) is > 80% of the lower limit of the normal range or < 70% of the lower limit if the CMAP amplitude is less than 80% of the lower limit.
- **Prolonged distal latency** is more than 125% of the upper limit of the normal range if the CMAP amplitude is more than 80% of the lower limit of the normal range or more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit.
- **An absent F wave or F-wave latency** is more than 125% of the upper limit if the CMAP amplitude is more than 80% of the lower limit or latency is more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit.

**** Consensus Criteria For The Diagnosis Of Multifocal Motor Neuropathy (American Association of Electrodiagnostic Medicine)**

- **Definite conduction block** is present in two or more nerves outside of common entrapment sites.* Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block. Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.
- **Probable conduction block** in two or more motor nerve segments that are not common entrapment sites, or Definite conduction block in one motor nerve segment and probable conduction block in a different motor nerve segment, neither of which segments are common entrapment sites. Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block, when this segment is technically feasible for study (that is, this is not required for segments proximal to axilla or popliteal fossa).

- Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested.
- The absence of each of the following upper motor neuronsigns: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.
 - *Median nerve at wrist; ulnar nerve at elbow or wrist; peroneal nerve at fibular head.

Rheumatologic Disorders

Condition	Criteria for Use
Dermatomyositis or Polymyositis	Treatment when ALL of the following are present <ul style="list-style-type: none"> • dermatomyositis or polymyositis established by biopsy • failure of standard medical therapy (at least a 4 month trial of corticosteroids and/or immunosuppressants) unless contraindicated. (IVIG may be covered after less than a four month trial of prednisone or prednisone combination therapies when there is profound, rapidly progressive and/or potentially life threatening muscular weakness refractory or intolerant to previous therapy). documented lack of response/poor response to prior therapies, as reflected by persistently elevated serum creatine kinase (CK) levels and/or lack of improvement on muscle strength improvement scales.
Kawasaki disease	Acute treatment when given in conjunction with aspirin within ten days of onset of symptoms

Infectious Disease

Condition	Criteria for Use
Staphylococcal or streptococcal toxic shock syndrome	Acute treatment for ANY of the following: <ul style="list-style-type: none"> • the infection is refractory to aggressive treatment • presence of an undrainable focus • persistent oliguria with pulmonary edema
HIV-positive children and adolescents who either have been exposed to measles or live in a high-prevalence measles area	Prevention of bacterial infections
Maternal-fetal transmission of HIV in women who are in their third trimester of pregnancy	When used in conjunction with antiretroviral treatment
Hepatitis A	Vaccination when intramuscular gammaglobulin is contraindicated
Tetanus	Vaccination when Tetanus Immune Globulin is unavailable
Varicella	Vaccination when Varicella Immune Globulin is unavailable

Dermatology

Condition	Criteria for Use
Autoimmune mucocutaneous blistering diseases; such as: <ul style="list-style-type: none"> ○ Pemphigus ○ Pemphigoid ○ Epidermolysis Bullosa 	Treatment when EITHER of the following criteria is met: <ul style="list-style-type: none"> • failure, contraindication or intolerance of conventional therapy [corticosteroids, azathioprine, cyclophosphamide, CellCept) • rapidly progressive disease in which a clinical

Condition	Criteria for Use
Acquisita	<p>response can not be affected quickly enough using conventional agents. In these situations, IVIG therapy should be given along with conventional treatment(s) and the IVIG used only until conventional therapy takes effect.</p> <p>Note: IVIG for the treatment of autoimmune mucocutaneous blistering disease is covered only for short-term therapy (no longer than 6 consecutive months) and not as a maintenance therapy.</p>

CIGNA HealthCare does not cover the use of intravenous immune globulin (human) (IVIG) for ANY of the following conditions because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- amyotrophic lateral sclerosis
- atopic dermatitis
- autoimmune neutropenia
- cellular immunodeficiencies including IFN, IL, CD4, NK
- chronic fatigue syndrome
- chronic mucocutaneous candidiasis (CMCC)
- complement deficiencies
- inclusion body myositis
- intractable pediatric epilepsy
- Lyme disease
- myasthenia gravis – chronic management
- clinically isolated syndrome-multiple sclerosis
- paraproteinemic demyelinating neuropathy (PDN)
- post-polio syndrome
- recurrent spontaneous miscarriage (primary)
- rheumatic fever
- Stevens-Johnson syndrome (bullous erythema multiforme)
- systemic lupus erythematosus
- toxic epidermal necrolysis

Standard Reference Ranges for Serum Immunoglobulin Levels

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

Normal Serum Immunoglobulin Levels (mg/dL)			
Age	IgA	IgG	IgM
0 – 30 days	1 – 7	611 – 1542	0 – 24
1 mo	1 – 53	241 – 870	19 – 83
2 mo	3 – 47	198 – 577	16 – 100
3 mo	5 – 46	169 – 558	23 – 85
4 mo	4 – 72	188 – 536	26 – 96
5 mo	8 – 83	165 – 781	31 – 103

6 mo	8 – 67	206 – 676	33 – 97
7 – 8 mo	11 – 89	208 – 868	32 – 120
9 – 11 mo	16 – 83	282 – 1026	39 – 142
1 yr	14 – 105	331 – 1164	41 – 164
2 yr	14 – 122	407 – 1009	46 – 160
3 yr	22 – 157	423 – 1090	45 – 190
4 yr	25 – 152	444 – 1187	41 – 186
5 – 7 yr	33 – 200	608 – 1229	46 – 197
8 – 9 yr	45 – 234	584 – 1509	49 – 230
10 yr & older	68 – 378	768 – 1632	60 – 263

Immunoglobulins, Serum Quantitative. Accessed April 6, 2009.
Available at: <http://www.aruplab.com/guides/ug/tests/0050630.jsp>

Standard Reference Ranges for Serum Immunoglobulin G Subclasses (1,2,3,4)

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

Normal Serum Immunoglobulin G Subclass Levels (mg/dL)				
Age	IgG 1	IgG 2	IgG 3	IgG 4
Cord Blood	435-1084	143-453	27-146	1-47
0-2 months	218-498	40-167	4-23	1-33
3-5 months	143-394	23-147	4-70	1-14
6-8 months	190-388	37-60	12-62	1-16
9-23 months	288-880	30-327	13-82	1-65
2 years	170-950	22-440	4-69	0-120
3-4 years	290-1065	28-315	4-71	0-90
5-6 years	330-1065	57-345	8-126	2-116
7-8 years	225-1100	42-375	9-107	0-138
9-10 years	390-1235	61-430	10-98	1-95
11-12 years	380-1420	73-455	16-194	1-153
13-14 years	165-1440	71-460	12-178	2-143
15 years & older	240-1118	124-549	21-134	7-89

Immunoglobulin G Subclass Levels (1,2,3,4). Accessed April 6, 2009.
Available at: <http://www.aruplab.com/guides/ug/tests/0050577.jsp>

General Background

Immune globulin intravenous (human) (IGIV) products are labeled for the treatment of primary immunodeficiency syndromes, idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, chronic lymphocytic leukemia (CLL), bone marrow transplantation (BMT), and pediatric HIV infection. Specific labeled uses vary for the individual products. All the available IGIV products are derived from pooled human plasma. All IGIV products are processed to remove as many viruses as possible. Each product undergoes two or more viral reduction methods. In addition, donors are carefully screened, and IGIV products are tested for significant viral pathogens.

Labeled Indications

- **Primary Immunodeficiency Diseases (PID):** Eight clinical trials have directly compared IGIV products with each other in adults and children with Primary Immunodeficiency Diseases. Five trials evaluated comparative clinical efficacy. In four trials, the products compared had equivalent efficacy at reducing the endpoints evaluated, including infection rate, prophylactic or therapeutic antibiotic use, physician and hospital visits, hospitalizations, and absenteeism. Only one trial found any differences between the products compared. There was a trend towards lower rate of the combined endpoint of sinus or pulmonary infection with Gamunex (12.3%) than Gamimune-N (23.3%, $p=0.06$ vs. Gamunex), along with a trend towards lower rate of acute sinusitis with Gamunex (5.5%) than Gamimune-N (13.6%, $p=0.092$ vs. Gamunex). Annual infection rate was significantly lower with Gamunex than Gamimune-N ($p=0.023$ vs. Gamunex). Gamimune-N is no longer marketed in the U.S., but has been replaced by Gamunex. Many of the studies enrolled small numbers of patients and may have lacked statistical power to detect small differences between the treatments.
- **Idiopathic Thrombocytopenic Purpura (ITP):** Three trials have evaluated the comparative efficacy of the individual IGIV products in patients with ITP. No trials have compared the efficacy of individual products that are currently marketed in the U.S. Two studies each enrolled fewer than 30 patients and reported few statistical comparisons, making it difficult to draw conclusions about comparative efficacy in chronic ITP. Bussel et al. (1988) compared Gamimune-N and Gamunex, using a dose of 1 g/kg/day IV for two consecutive days. The trial enrolled 97 patients, although only 81 patients were included in the efficacy analysis, including 30 patients with acute ITP and 51 patients with chronic ITP. Patients were also stratified by age, including children under age 11 ($n=13$), children between ages 11–18 ($n=7$), and adults ($n=61$). However, too few patients were enrolled to make comparisons between Gamimune-N and Gamunex for the individual subgroups. Similar numbers of patients responded to therapy with Gamimune-N (83%) or Gamunex (90%, NS), achieving platelet counts of 50,000 cells/mm³ within seven days after dosing. The number of patients maintaining platelet counts of at least 50,000 cells/mm³ for at least seven days was also similar for Gamimune-N (60%) and Gamunex (75%, NS). Fewer patients needed corticosteroids for more than seven days after Gamunex (47%) than Gamimune-N (25%, $p=0.02$). Similar numbers of patients in each group experienced clinically significant bleeding. Gamimune-N is no longer marketed in the U.S., but has been replaced by Gamunex.

Wolff et al. (1999) compared Sandoglobulin and Carimune NF in adults ($n=27$), both given at a dose of 400 mg/kg/day IV for five consecutive days. Seventy-five percent of patients (12/16) responded to Sandoglobulin, achieving a platelet count above 50,000 cells/mm³ at study end, compared to 100% (10/10) of Carimune NF patients ($p=0.123$ vs. Sandoglobulin). Time to response, duration of response, and percent of patients with persistent bleeding were similar with both products, although no statistical comparisons were reported. Sandoglobulin is no longer marketed in the U.S., but has been replaced by Carimune NF.

In one comparative study, the efficacy of Intraglobin 400 mg/kg/day IV for five consecutive days and Venoglobulin-I 1 g/kg/day IV for two days was studied in children ($n=17$). No patients in either group were classified as excellent responders (i.e., reaching a platelet count above 100,000 cells/mm³ within four weeks and maintaining that through study end). Thirty percent of Intraglobin-treated patients and 86% of Venoglobulin-I-treated patients were considered good responders, achieving a platelet count above 100,000 cells/mm³ within four weeks but below 100,000 cells/mm³ at study end. The remaining patients in each group were considered fair responders, with platelet count increasing but remaining below 100,000 cells/mm³. No statistics were reported for either endpoint.

- Kawasaki Disease:** One observational trial has compared the efficacy of Iivegam and Venoglobulin-I 2 g/kg/day IV for one day in children with Kawasaki Disease diagnosed within 10 days of study enrollment. All but one Iivegam patient had coronary artery abnormalities at baseline. The risk of developing coronary artery abnormalities after disease onset was similar with Iivegam (7%, 3/45) and Venoglobulin-I (11%, 5/45, OR 1.75, 95% CI 0.39–7.8, NS between groups). The percentage of patients with fever on day 3 after IGIV therapy was also similar for Iivegam (27%) and Venoglobulin-I (33%, NS).

A Cochrane systematic review has been published, evaluating 16 clinical trials comparing various doses of IGIV with aspirin in children with Kawasaki Disease diagnosed within ten days of study enrollment. The total IGIV dose ranged from 100 mg/kg as a single dose to 2 g/kg given over 1–5 days. A variety of IGIV preparations were used, including pepsin-treated, intact, polyethylene glycol-treated, and sulfonated products. However, no specific product names were reported. Results were reported separately for the entire study group and for those patients without coronary artery abnormalities at baseline.

In the entire study group, IGIV was more effective than aspirin at reducing coronary artery abnormalities at day 30. On day 30 after treatment, patients treated with IGIV were less likely to develop new coronary artery abnormalities compared to those given aspirin (RR 0.74, 95% CI 0.61–0.9, $p < 0.05$ between groups). There was no difference in risk of new coronary artery abnormalities on day 60 with IGIV compared with aspirin (RR 0.75, 95% CI 0.51–1.1, NS). The risk of new coronary artery abnormalities at day 30 was lower with IGIV 2 g/kg as a single dose compared with IGIV 2 g/kg given over five days (RR 0.22, 95% CI 0.08–0.64, $p < 0.05$ between groups). In general, higher doses of IGIV were more effective than lower doses. There was also a trend towards shorter duration of fever with IGIV than aspirin (weighted mean difference [WMD] 0.66 days, 95% CI -4.99 to +6.31, NS). No efficacy or safety differences were noted between individual IGIV preparations. However, there was significant heterogeneity of effect in trials using different IGIV doses.

Results were similar in the subgroup of patients without coronary artery abnormalities at baseline. On day 30, patients were less likely to have new coronary artery abnormalities with IGIV than aspirin (RR 0.67, 95% CI 0.46–1.0, $p < 0.05$). On day 60, there was a trend towards lower risk of new abnormalities with IGIV than aspirin (RR 0.57, 95% CI 0.29–1.12, $p = 0.06$).

- Prevent Infection in Chronic Lymphocytic Leukemia (CLL):** The comparative efficacy of the available IGIV products for this use has not been assessed in published individual trials, Cochrane systematic reviews, or meta-analyses. Instead, three trials were included comparing IGIV with placebo (albumin, normal saline) or no treatment. The specific products evaluated were Sandoglobulin, Gammagard, and Ig-Vena N. After six months of therapy, more patients remained free of infections with IGIV (67%) than no treatment (30%, $p < 0.01$). More patients remained infection-free at 12 months with IGIV (76%) than no treatment (35%, $p < 0.02$). More patients remained free of serious infections with IGIV (50%) than placebo (8.3%, $p = 0.003$) during one year of therapy. The number of patients with at least three infections was lower with IGIV (29%) than placebo (61%, $p = 0.04$), as was the number of patients with at least three serious infections (IGIV 21%, placebo 56%, $p = 0.02$). The risk of infection increased as serum IgG concentration decreased. Serious infections were more likely when serum IgG concentration fell below 6.4 g/L ($p = 0.046$ vs. higher IgG concentration).
- Prevent Complications of Bone Marrow Transplantation:** Two clinical trials have directly compared IGIV products with each other in children and adults undergoing BMT. Both trials evaluated enrolled only cytomegalovirus (CMV)-seronegative patients. Only one trial assessed clinical efficacy. At both three and 12 months, risk of CMV infection was similar with American Red Cross brand IGIV, Gamimune-N, Gammagard, and Sandoglobulin. Titers of CMV antibody were also similar with all four products. Both CMV neutralizing antibody and CMV enzyme-linked immunosorbent assay (ELISA) titers were highest with Gammagard, followed by American Red Cross brand and Sandoglobulin, and lowest with Gamimune-N ($p < 0.05$ for all comparisons). Serum trough IgG concentrations were similar in all treatment groups.

A Cochrane systematic review has been published, evaluating 12 clinical trials of conventional IGIV, CMV-hyperimmune IGIV, or no treatment in patients undergoing BMT. Trials enrolled both CMV-seronegative and CMV-seropositive patients. The authors did not report which IGIV preparations were used or the doses administered. Results were reported separately for the entire study group, CMV-seronegative patients, and CMV-seropositive patients. Median duration of follow-up was five months.

In the entire study group, any IGIV (conventional or CMV-hyperimmune) was more effective than no treatment. Compared to untreated controls, total mortality was lower with any IGIV ($p < 0.05$) or CMV-hyperimmune IGIV but was unchanged with conventional IGIV. Risk of fatal CMV infection was lower with any IGIV compared with control ($p < 0.05$). Compared with control, there was a trend towards reduced risk of symptomatic CMV infection with any IGIV and a significantly lower risk with conventional IGIV but no difference in risk CMV-hyperimmune IGIV. Risk of CMV pneumonia was lower with any IGIV ($p < 0.05$) or conventional IGIV but was unchanged with CMV-hyperimmune IGIV. Risk of non-CMV pneumonia was reduced with any IGIV ($p < 0.05$), conventional IGIV, and CMV-hyperimmune IGIV. There was a trend towards lower risk of acute GVHD with any IGIV.

In CMV-seronegative patients, risk of symptomatic CMV infection was significantly lower with any IGIV than control ($p < 0.05$). Risk of non-CMV pneumonia was also lower with any IGIV than control ($p < 0.05$). In CMV-seropositive patients, there was no difference between any IGIV and control in the risk of symptomatic CMV infection. However, the risk of non-CMV pneumonia was significantly lower with any IGIV than control ($p < 0.05$).

- **Pediatric HIV Infection:** The American Academy of Pediatrics (2003) and the United States Public Health Service/IDSA (2002) have published guidelines for preventing opportunistic infections in these children. Because antiretroviral agents reduce infection and prolong survival, they are considered the mainstay of therapy and are indicated for most patients.

The comparative efficacy of the available IGIV products for this use has not been assessed in published individual trials, Cochrane systematic reviews, or meta-analyses. Instead, two trials were included comparing IGIV (Gammagard) with placebo (albumin). The results of these trials suggest that IGIV reduces the risk of bacterial infection, viral infection, and hospitalization but does not impact survival. Patients with CD4+ counts of 200 cells/mm³ or greater are more likely to benefit from IGIV than those with CD4+ counts below 200 cells/mm³, regardless of whether or not the patient has been diagnosed with acquired immunodeficiency syndrome (AIDS). Patients receiving cotrimoxazole prophylaxis are less likely to benefit, compared to those not receiving cotrimoxazole prophylaxis.

The National Institute of Child Health and Human Development (NICHD) Intravenous Immunoglobulin Study Group conducted the largest trial, enrolling 372 children with HIV infection. Several subgroup analyses have also been published. In the initial study, the mean duration of follow-up was 16.4 months. Patients were randomized in two subgroups—those with either CD4+ count of below 200 cells/mm³ or with AIDS at enrollment, and those with CD4+ count at least 200 cells/mm³ without AIDS at enrollment. In the entire study group, IGIV reduced the risk of bacterial infections more than placebo. In patients with CD4+ count of at least 200 cells/mm³ (with or without AIDS), IGIV reduces the risk of minor bacterial infection, serious bacterial infection, viral infection, and hospitalization compared to placebo but does not impact overall survival. In the same subgroup, the age-adjusted CD4+ count decreased 13.5 cells/mm³/month more slowly with IGIV than placebo (95% CI for difference 3.1–23.9, $p = 0.012$) during a mean of 18.3 months follow-up. The positive effect of Gamimune-N on CD4+ count increased with time. In patients with CD4+ count below 200 cells/mm³ (with or without AIDS), there was no difference between IGIV and placebo overall survival, risk of any bacterial infection, or hospitalization rate, although there was a trend towards lower rate of serious infection. One subgroup analysis evaluated patients with at least one sinusitis episode during the trial and found no difference between Gamimune-N and placebo in the rate of sinus infections.

The NICHD Intravenous Immunoglobulin Study Group also evaluated the long-term efficacy of IGIV in an open-label extension. After completion of the double-blind trial, 148 children were given open-label IGIV for a mean of 16 months. In 67 patients originally allocated to placebo, the rate of serious bacterial infections was significantly lower after switching to open-label Gamimune-N (16.3/100 patient-years) compared to placebo (32.1/100 patient-years, difference 15.8, 95% CI for difference 3.2–28.5, $p=0.014$). Minor bacterial infections were also lower with open-label Gamimune-N (63.9/100 patient-years) than placebo (125/100 patient-years, difference 61.2, 95% CI for difference 29.2–93.3, $p<0.001$). The rates of viral infections, opportunistic infections, and hospitalizations were numerically lower with Gamimune-N but did not reach statistical significance compared with placebo. Benefit was seen with open-label Gamimune-N regardless of concomitant cotrimoxazole use. In patients originally allocated to IGIV, there was no change in any endpoint with open-label Gamimune-N compared to blinded Gamimune-N.

The second trial was conducted by the Pediatric AIDS Clinical Trial Group. The mean duration of follow-up was 25.5 months. Patients were randomized in two subgroups based on whether or not they were receiving cotrimoxazole prophylaxis at enrollment. Table 6 summarizes key results. In the entire study group, IGIV reduced the risk of bacterial infections and the risk of hospitalizations more than placebo but did not impact overall survival. The CD4+ count decreased at a similar rate with Gamimune-N (1.07% per week) and placebo (0.92% per week, NS). In patients receiving cotrimoxazole prophylaxis, there was no difference between IGIV and placebo in the risk of any bacterial infection, serious bacterial infection, hospitalization, and overall survival. There was a trend towards lower rate of minor bacterial infections with IGIV, but this did not reach significance. In patients not receiving cotrimoxazole prophylaxis, IGIV significantly reduced the rates of any bacterial infection and serious bacterial infection but did not impact overall survival.

Unlabeled indications included in criteria: Based on peer-reviewed literature and the pharmaceutical compendium of drug information from the American Society of Health-System Pharmacists (AHFS), there is sufficient evidence to support the use of IGIV for the following indications.

- **Infection Prophylaxis and Treatment in Neonates**

- **Infection Prophylaxis:** No head-to-head trials have directly compared the individual IGIV products for this use. However, a Cochrane systematic review and a meta-analysis have evaluated the efficacy of IGIV for preventing infection in preterm or low birth weight infants. Based on these analyses, IGIV appears to be effective for reducing sepsis and serious infection. It remains unclear whether IGIV prophylaxis improves survival.

The Cochrane systematic review included 19 trials comparing IGIV with placebo (albumin, dextrose, saline, sucrose) or no treatment. The total IGIV dose ranged from 120 mg/kg to 5 g/kg, given as a single dose or repeated every 7–21 days. A variety of IGIV preparations were used, including Gammagard, Sandoglobulin, Gamimune-N, Intraglobin, Ig-Vena, and Venogamma. Compared to controls, risk of sepsis was lower with IGIV ($p<0.05$) with an absolute risk reduction of -0.03 (95% CI 0 to -0.05), giving an NNT of 33. Risk of serious infection was lower with IGIV ($p<0.05$ between groups) with an absolute risk reduction of -0.04 and an NNT of 25. There was no difference between IGIV and control in risk of necrotizing enterocolitis, intraventricular hemorrhage, all-cause mortality, infection-related mortality, or length of hospital stay. The authors noted significant heterogeneity for the endpoints of sepsis and serious infection, which may have been caused by differences in IGIV dosage regimens. The meta-analysis included 12 trials comparing IGIV with placebo (not specified) or no treatment. The total IGIV dose ranged from 120 mg/kg to 5 g/kg, given as a single dose or repeated every 14–21 days. A variety of IGIV preparations were used, including Gammagard, Sandoglobulin, Gamimune-N, Intraglobin, and Venogamma. IGIV reduced total mortality compared to control ($p=0.0193$), although study heterogeneity was too great to calculate a pooled odds ratio. Significant heterogeneity remained even when data were reanalyzed by type of IGIV preparation used.

- **Treatment of Infection:** One trial has directly compared IGIV products with each other, although neither product is available in the U.S. Patients were given Intraglobin or Pentaglobin 250 mg/kg/day IV for four days, starting therapy as soon as infection was suspected. In patients with proven sepsis, all-cause mortality was similar with Intraglobin (14.2%) and Pentaglobin (6.8%, NS vs. Intraglobin). All-cause mortality was numerically higher with Intraglobin (15.8%) than Pentaglobin (6.8%) in patients with proven or suspected sepsis; no statistics were reported for this comparison. Leukopenia resolved slightly faster with Intraglobin (29.6 days) than Pentaglobin (19.1 days), although no statistics were reported for this comparison. The ratio of immature to total neutrophils normalized more quickly with Intraglobin (51 days) than Pentaglobin (35.1 days, $p < 0.05$ vs. Intraglobin). This study enrolled small numbers of patients and may have lacked statistical power to detect small differences between groups for some endpoints. A Cochrane systematic review and a meta-analysis have also evaluated the efficacy of IGIV for this indication. The Cochrane systematic review included nine trials comparing IGIV to placebo (albumin, dextrose, maltose, saline or no treatment in term or preterm infants). The total IGIV dose ranged from 500 mg/kg to 6 g (not based on weight). A variety of IGIV preparations were used, including Sandoglobulin, Gamimune-N, Intraglobin, and Pentaglobin. Compared to controls, all-cause mortality in suspected infection was lower with IGIV ($p = 0.05$), with an absolute risk reduction of -0.09. Treatment with IGIV also reduced all-cause mortality in proven infection compared to control ($p = 0.04$). There was no difference in hospital length of stay for term or preterm infants. There was significant heterogeneity in length of stay for term infants but not in mortality or length of stay for preterm infants. Heterogeneity may have been caused by differences in IGIV dosage regimens. The meta-analysis included three trials comparing IGIV to placebo (not specified) or no treatment. The total IGIV dose ranged from 500 mg/kg to 6 g (not based on weight). The trials used two IGIV preparations; Sandoglobulin and Pentaglobin. Total mortality was significantly lower with IGIV ($p = 0.007$) compared to control. No significant heterogeneity was noted.
- **Neonatal Isoimmune Hemolytic Disease:** Five controlled clinical trials have evaluated IGIV in neonatal isoimmune hemolytic disease. All found a significant benefit when IGIV was added to phototherapy, compared to phototherapy alone. The IGIV doses given ranged from 500–1,000 mg/kg given as a single dose, to 500–800 mg/kg/day for three days. In a Cochrane systemic review of the three single-dose trials (189 patients), 15% of patients given IGIV needed blood exchange transfusions, compared to 52% of patients given phototherapy alone (relative risk 0.28, 95% CI 0.17–0.47, number needed to treat 2.7). The fourth trial (37 patients) did not report number of blood exchange transfusions but did report a lower rate of total blood transfusions with IGIV (42%) compared to phototherapy alone (67%, $p < 0.05$). In the final trial (61 patients), fewer infants required exchange transfusion with a three-day IGIV course (0%, $p < 0.05$ vs. both other groups) compared to either a one-day IGIV course (15%, $p < 0.05$ vs. phototherapy alone) or phototherapy alone (33%). In two of the included trials, the addition of IGIV significantly reduced mean duration of hospitalization ($p < 0.05$ vs. phototherapy alone). Case reports and case series were not reviewed for this indication.
- **Infection Prophylaxis in Multiple Myeloma:** Two randomized clinical trials have evaluated IGIV for infection prophylaxis in patients with multiple myeloma. In the largest trial ($n = 83$), the incidence of serious infections was significantly lower with IGIV 400 mg/kg every four weeks (0.042 infections/patient-month) than placebo (0.081 infections/patient-month, $p = 0.02$). This reduction corresponds to a number needed to treat of 2.2 patients to prevent one serious infection per patient-year. When analyzed by specific infection type, IGIV significantly reduced the risk of septicemia, pneumonia, and non-pneumonia chest infections compared to placebo ($p < 0.05$ for all subgroups). The risk of urinary tract infection and other serious infections was similar in both treatment groups. Mortality data were not evaluated due to the study's relatively short duration of 12 months.

The second trial followed 25 patients for 24 months and found similar results. There were fewer serious infections with IGIV 300 mg/kg every four weeks (0.038 infections/patient-month) than no

therapy (0.12 infections/patient-month, $p < 0.002$). However, the incidence of minor infections was similar with IGIV (0.088 infections/patient-month) and no therapy (0.108 infections/patient-month).

- **Prevent Complications of Hematopoietic Stem Cell Transplantation (HSCT):** The Centers for Disease Control (CDC) have established guidelines that recommend use of IGIV to prevent bacterial infections (e.g., *Streptococcus pneumoniae* sinopulmonary infections) in allogeneic HSCT recipients who experience severe hypogammaglobulinemia (i.e., Immunoglobulin G [IgG] less than 400 mg/dL) within the first 100 days after transplant. The CDC guidelines also state that in the absence of severe demonstrable hypogammaglobulinemia (i.e., IgG levels < 400 mg/dL, which might be associated with recurrent sinopulmonary infections), routine monthly IGIV administration to HSCT recipients > 90 days after HSCT is not recommended as a means of preventing bacterial infections.
- **Allosensitized Solid Organ Transplants:** Two controlled trials have evaluated IGIV in allosensitized patients undergoing transplantation. These trials suggest IGIV improves outcomes in allosensitized cardiac transplant patients and may improve transplantation rates in highly-sensitized patients awaiting renal transplantation. In the first trial, allosensitized patients received plasmapheresis followed by IGIV 20 g as a single dose immediately prior to cardiac transplantation, while unsensitized patients received no intervention. At baseline, more allosensitized patients had positive cross matches, pulmonary hypertension, and required mechanical circulatory support ($p < 0.05$ vs. unsensitized patients for each). There was no difference between allosensitized and unsensitized patients in post-transplant length of stay, one-year survival, or risk of rejection.

A second trial evaluated IGIV 2 g/kg monthly for four months in allosensitized patients awaiting renal transplantation. More patients were able to receive transplants after IGIV (35%) than placebo (20%, one-tailed $p = 0.069$), although this trend did not achieve statistical significance. When only cadaveric transplants were considered, more patients were transplanted after IGIV (31%) than placebo (12%, one-tailed $p = 0.0137$). When stratified by prior transplantation status, transplantation was more likely with IGIV than placebo, both in patients with prior transplants (IGIV 22%, placebo 7%, two-tailed $p = 0.047$) and in those without prior transplants (IGIV 50%, placebo 28%, two-tailed $p = 0.047$). Therapy with IGIV reduced projected mean time to transplantation (4.8 years) compared to placebo (10.3 years, one-tailed $p = 0.049$). After transplantation, there was no difference between IGIV and placebo in graft failure, graft survival rate, or serum creatinine concentration of viable grafts. However, acute rejection episodes were more common with IGIV (53%) than placebo (10%, $p = 0.042$).

Several case reports noted beneficial effects in allosensitized patients awaiting solid organ transplant with a variety of IGIV regimens, including 2 g/kg as a single dose prior to transplantation, plasmapheresis followed by 20 g as a single dose prior to transplantation, 500 mg/kg once weekly until transplantation, or 10 g every three weeks until transplantation.

- **Fetal Alloimmune Thrombocytopenia:** Two randomized clinical trials, one Cochrane systematic review, and three observational trials have evaluated IGIV in this disorder. Bussel et al. (1996) conducted an open-label experimental trial, randomizing 54 women to therapy with IGIV 1 g/kg weekly plus oral dexamethasone 1.5 mg/day or monotherapy with IGIV 1 g/kg weekly. Fetal platelet counts were similar with IGIV alone or with the combination, both during pregnancy and at birth. No intracranial hemorrhages occurred in either treatment group.

Berkowitz et al. (2006) conducted a parallel, randomized, multicenter study that stratified 79 patients to two different treatment arms based on the presence of a peripartum intracranial hemorrhage in a previously affected sibling and/or the initial fetal platelet count. Forty women whose children from a previous birth had a peripartum intracranial hemorrhage or whose current fetus had an initial platelet count less than $20,000/\text{mL}^3$ were randomly assigned to receive IGIV plus prednisone or IGIV alone. The mean increase in fetal platelet counts in the following three to eight weeks was $67,100/\text{mL}^3$ and $17,300/\text{mL}^3$, respectively ($p < 0.001$). Thirty-nine patients whose previously affected child did not have an intracranial hemorrhage and whose current fetus had an initial platelet count of more than $20,000/\text{mL}^3$ were randomly assigned to receive IGIV alone or

prednisone alone. In this group, there were no significant differences, and 33 (85%) had birth platelet counts more than 50,000/mL³.

In one observational follow-up trial in 37 women with documented fetal or neonatal alloimmune thrombocytopenia, therapeutic failure occurred in 33% of IGIV-treated pregnancies compared to 70% of corticosteroid-treated pregnancies (no statistics reported). Therapeutic success occurred in 26% of pregnancies with IGIV and 10% with corticosteroids (no statistics reported). In the other two observational follow-up trials (61 patients), pregnant mothers served as their own historical controls, comparing results after IGIV therapy to outcomes of their earlier pregnancy. Intracranial hemorrhage occurred in 0/28 (0%) pregnancies treated with IGIV compared to 13/33 (39%) of the earlier pregnancies.

A Cochrane systematic review has been published, evaluating one clinical trial comparing the efficacy of IGIV plus dexamethasone versus IGIV alone. No significant differences were reported between the treatment and control groups in any outcome measured: mean platelet count at birth (weighted mean difference (WMD) $14.10 \times 10^9/L$, 95% confidence interval (CI) -30.26 to 58.46), mean gestational age at birth (WMD -0.50 weeks, 95% CI -2.69 to 1.69), mean rise in platelet count from first to second fetal blood screen (WMD $-3.50 \times 10^9/L$, 95% CI -24.62 to 17.62) and mean rise in platelet count from birth to first fetal blood screen (WMD $24.40 \times 10^9/L$ (95% CI -14.17 to 62.97)). However, the authors noted that, although this trial had adequate methodological quality, the method used to calculate sample size was inappropriate; therefore, the power calculation was not sufficient to determine any significance in differences between the treatment groups. The authors concluded that, although no randomized controlled trials have been conducted to investigate the role of intravenous immunoglobulin, data from observational studies have suggested an improvement in clinical outcome and probable reduction in risk for intracranial hemorrhage when intravenous immunoglobulin is administered to the mother throughout pregnancy. Furthermore, the authors noted that practice has evolved such that intravenous immunoglobulin is currently first-line treatment in the antenatal management of fetal alloimmune thrombocytopenia.

American College of Obstetricians and Gynecologists (ACOG) guidelines also recommend that neonatal alloimmune thrombocytopenia should be treated with IGIV as the initial approach when fetal thrombocytopenia is documented.

- **Chronic Parvovirus B19 Infection:** There are no published clinical trials evaluating the efficacy of IGIV for this indication. Six case series describe the use of IGIV for chronic parvovirus B19 infection in a total of 27 patients. Therapy with IGIV 1-2 g/kg (divided and given over 1–10 days) consistently induced symptom resolution and improved anemia. Remissions lasted from one month to four years, although many patients relapsed without additional IGIV. Many of the included patients had experienced parvovirus symptoms for a prolonged duration (12–24 months) but these resolved within 2–4 weeks of IGIV therapy. Four of these case series included AIDS patients, as symptomatic parvovirus B19 infection is rare in patients with healthy immune systems. The results of these case series are consistent with multiple single case reports which are not included in the evidence tables.
- **Guillain-Barré Syndrome**
 - **Acute Inflammatory Demyelinating Polyneuropathy (AIDP):** The American Academy of Neurology has published treatment guidelines (2003). There is no cure for AIDP. Treatment consists of supportive care, physical therapy, and immune modulating therapy (i.e., plasmapheresis or IGIV). Both plasmapheresis and high-dose IGIV significantly speed recovery when performed within two weeks of symptom onset. Although the treatments are equal in efficacy, IGIV is easier to administer and may be preferred. The usual IGIV regimen is 400 mg/kg/day IV for five days. Relapse may occur 1–2 weeks after initial therapy and may be treated with a repeat course of the initial therapy. Sequential treatment with plasmapheresis and IGIV does not improve outcomes and is not recommended. Corticosteroids are not recommended. Cochrane systematic review has evaluated the efficacy of IGIV in patients with AIDP of less than two weeks' duration.

The Cochrane systematic review included nine trials comparing IGIV to plasma exchange, plasma exchange followed by IGIV, immunoadsorption, immunoadsorption followed by IGIV, or supportive care. The total IGIV dose ranged from 1.2–2.4 g/kg. The authors did not report which specific IGIV preparations were used. There was no difference between IGIV and plasma exchange in disability improvement at four weeks, time until patient could walk unaided, time until patient could breathe without ventilator, mortality, or the combined endpoint of death or disability at 12 months. In children, the time to bulbar/respiratory recovery or two-grade improvement in muscle strength was shorter with IGIV (17 days) than plasma exchange (30 days, $p < 0.0001$). Risk of adverse effects was similar with IGIV and plasma exchange, but IGIV patients were less likely to discontinue therapy ($p = 0.0001$ vs. plasma exchange). There was no difference between IGIV and immunoadsorption in disability improvement at four weeks or mortality. Studies comparing IGIV with supportive care could not be pooled and did not evaluate specified outcomes. Compared to lower IGIV doses (1.2 g/kg), higher IGIV doses (2.4 g/kg total) did not significantly improve disability at four weeks, mortality, or chance of full recovery at 12 months. There was a trend towards shorter time until patients could walk unaided with high-dose IGIV (84 days) than low-dose IGIV (131 days, $p = 0.08$). Combining IGIV with other immunomodulatory treatments does not significantly improve efficacy. Compared to plasma exchange alone, the addition of IGIV to plasma exchange did not significantly affect disability improvement at four weeks, time until patient could walk unaided, time until patient could breathe without ventilator, mortality, or the combined endpoint of death or disability at 12 months. Similarly, the addition of IGIV to immunoadsorption was no more effective than immunoadsorption alone for improving disability at 12 months or mortality, although disability improved more at four weeks with combination therapy ($p = 0.004$ vs. immunoadsorption alone).

- **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):** The National Institute of Neurological Disorders and Stroke (NINDS) recommends IGIV as first-line therapy, followed by plasmapheresis or corticosteroids. The usual dose is IGIV 400 mg/kg/day IV for five days, with the treatment courses repeated at approximately six-week intervals. In refractory disease, corticosteroids may be combined with other immunosuppressants (e.g., azathioprine, cyclophosphamide, methotrexate, cyclosporine). A total of six trials have compared IGIV with plasma exchange, prednisolone, or placebo. The total IGIV dose ranged from 1.8–2.4 g/kg. The authors did not report which specific IGIV preparations were used. There was no difference between IGIV and plasma exchange in disability improvement at six weeks, improvement in weakness, or change in summated compound muscle action potential (CMAP). Compared to prednisolone, IGIV caused similar improvements in disability at two and six weeks, muscle strength, median nerve distal CMAP amplitude, or median nerve conduction velocity. There was a trend towards higher rate of adverse effects with IGIV (60%) than prednisolone (41%, $p = 0.16$). Disability was more likely to improve significantly within one month with IGIV (47%) than placebo (15%, $p = 0.0002$) with a number needed to treat (NNT) of three. Magnitude of improvement in disability was greater with IGIV than placebo ($p < 0.05$ vs. IGIV). Compared to placebo, IGIV caused similar improvements in muscle strength, median nerve distal CMAP amplitude, and median nerve distal motor latency. Mean median nerve conduction velocity improved more with IGIV than placebo ($p = 0.03$ vs. IGIV). Risk of adverse effects was similar with IGIV and placebo.
- **Treatment of Acute Myasthenic Crisis with Decompensation:** Few well-designed clinical trials have been published on this disorder. A 2006 Cochrane systematic review of five trials has evaluated short-term efficacy of IGIV (up to 16 weeks). The reviewers stated that the methodologic quality of the included trials was debatable. Results could not be pooled and no meta-analysis was performed. However, in two trials evaluating IGIV efficacy for disease exacerbation, there was no difference between IGIV and methylprednisolone or plasma exchange in effects on muscle strength/fatigue. Another trial evaluating IGIV efficacy for disease exacerbation showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IGIV. The other two trials evaluated efficacy for chronic stable disease and found no difference between IGIV and plasma exchange or placebo in effects on activities of daily living or muscle

strength/fatigue. The IGIV regimens given included 400 mg/kg/day for 3–5 days, 1 g/kg/day for one day, 1 g/kg/day for two days, and 30 g/day for five days.

The American Hospital Formulary Service (AHFS) Drug Information[®] states that IGIV may be beneficial in myasthenia gravis patients with acute severe decompensation when other treatments have been unsuccessful or are contraindicated.

- **Lambert-Eaton Myasthenic Syndrome (LEMS):** Cochrane systematic review and a placebo-controlled trial have evaluated the efficacy of IGIV in patients with LEMS. The Cochrane systematic review included three trials evaluating the efficacy of IGIV, 3, 4-diaminopyridine, or placebo in patients with LEMS with or without small-cell lung cancer. One included trial evaluated the efficacy of IGIV 2 g/kg (total dose), although the specific preparation was not reported. No meta-analysis could be performed, since only one trial was included. Muscle strength and mean resting CMAP improved slightly more with IGIV than placebo, but this difference did not reach statistical significance. Compared to placebo, 3, 4-diaminopyridine caused greater improvement in mean resting CMAP ($p < 0.05$ vs. placebo).

One crossover trial compared IGIV with placebo in patients with LEMS without small-cell lung cancer. Patients were given a single course of placebo or IGIV 1 g/kg/day IV for two days, followed by an eight-week washout before crossover. In the IGIV arm, patients could receive either Flebogamma (as Alphaglobin) or Gammagard although no comparisons were made between these two products. Eighty percent of patients given IGIV reported increased strength at two weeks (no statistical comparison reported). Compared with placebo (no values reported), IGIV caused greater improvements in limb strength (improved 20%, $p = 0.038$ vs. placebo), vital capacity (improved 8%, $p = 0.028$ vs. placebo), drinking time (improved 15%, $p = 0.017$ vs. placebo), and antibody titer ($p = 0.028$ vs. placebo). There was a trend towards greater improvement in mean resting CMAP with IGIV ($p = 0.066$ vs. placebo). Calcium-channel antibodies decreased more with IGIV at weeks 4–6 ($p < 0.05$ vs. placebo), then slowly began increasing. There was no evidence that IGIV directly neutralizes calcium-channel antibodies.

- **Multifocal Motor Neuropathy:** The comparative efficacy of the available IGIV products for this use has not been assessed in published individual trials, Cochrane systematic reviews, or meta-analyses. Instead, four placebo-controlled trials were included evaluating the short-term efficacy of various IGIV preparations including Endobulin, Gamimune-N, Dutch Central Laboratory Blood Transfusion IGIV, and French National Center for Blood Transfusion IGIV. Based on these trials, IGIV is more effective than placebo at improving functional ability and may also improve muscle strength and nerve function. Seventy-eight to 100% of patients responded to IGIV therapy. Treatment with IGIV is effective in both newly-diagnosed patients and those who have relapsed after prior response to IGIV therapy. Response to IGIV therapy correlates inversely with age, with responders being much younger (mean 33.1 years) than nonresponders (mean 51.8 years, $p = 0.0014$). Two trials found IGIV had no effect on conduction block, while a third trial reported decreased conduction block after IGIV. Antibody titers to ganglioside GM1 are not routinely affected by IGIV.
- **Relapsing-Remitting Multiple Sclerosis (RRMS):** The meta-analysis included four trials evaluating the efficacy of IGIV or placebo in patients with RRMS ($n = 260$) or secondary progressive multiple sclerosis (SPMS) ($n = 5$). The IGIV dose varied from 150–2,000 mg/kg IV every month to 400 mg/kg IV every two months. The specific preparation used was not reported. Disability improved more with IGIV than placebo ($p = 0.042$). Patients were 11% less likely to report worsening of disability after IGIV than placebo ($p = 0.03$), although there was significant heterogeneity between studies. Patients were 16% more likely to report improvement of disability after IGIV than placebo ($p = 0.006$); there was significant heterogeneity between studies. The annual relapse rate was lower with IGIV than placebo ($p = 0.00003$). Compared to placebo, 29% more IGIV-treated patients were relapse-free at the study's end ($p < 0.05$).

The Cochrane systematic review included two trials evaluating the efficacy of IGIV or placebo in patients with RRMS. Although the authors planned to include trials of both RRMS and SPMS, no

published trials were available for SPMS. The IGIV dose varied from 150–200 mg/kg IV every month to 400 mg/kg IV every two months. The specific IGIV preparation used was not reported. No meta-analysis could be performed, since only two trials were included. Disability improved more with IGIV than placebo ($p=0.008$). Fewer patients reported worsening of disability after IGIV (13%) than placebo (17%, $p=0.03$). The reported relapse rates were lower with IGIV (range: 0.52–0.59 relapses/year) than placebo (range: 1.26–1.61 relapses/year, $p<0.05$ in both included trials). At the study's end, more patients were relapse-free with IGIV (range: 30–53%) than placebo (range: 0–36%, $p<0.05$ in both included trials). Time to first relapse was longer with IGIV (range: 233–237 days) than placebo (range: 82–151 days) in one trial but was similar in the other study.

A study compared IGIV 400 mg/kg/day IV for five days each month to placebo in 24 patients with RRMS. The specific IGIV preparation used was not reported, and the authors did not report any statistical comparisons between treatment groups. Disability score improved with IGIV but worsened with placebo. Fewer numbers of patients reported disease worsening with IGIV (8.3%) than placebo (25%). Greater numbers of patients reported disease improvement with IGIV (25%) than placebo (8.3%). The change in disability score correlated with the size and number of brain lesions. There was a significant negative correlation with IGIV ($p=0.022$) and a significant positive correlation with placebo ($p=0.014$), suggesting that magnetic resonance imaging (MRI) may be more useful than disability score for detecting early beneficial effects of IGIV. After treatment, both the number and volume of brain lesions decreased significantly from baseline with IGIV but increased significantly with placebo.

- **Stiff Person Syndrome:** Randomized clinical trials have evaluated IGIV for stiff person syndrome. One placebo-controlled trial ($n=16$) has been published evaluating IGIV for this indication. Overall stiffness improved significantly with IGIV 1 g/kg/day IV for two days each month ($p=0.01$ vs. placebo). A subgroup analysis found that IGIV significantly reduced stiffness in the abdomen, trunk, and face ($p<0.01$ vs. placebo for each site). Frequency of spasms was also reduced significantly with IGIV ($p=0.03$ vs. placebo). Eleven of 14 patients improved with IGIV, while none improved and four patients worsened with placebo. Thirteen of 14 patients requested additional IGIV treatments after the study ended. The investigators noted a significant carryover effect when IGIV was given first. Anti-GAD65 antibodies decreased from baseline with IGIV, although antibody titers did not correlate with either disease severity or magnitude of response to IGIV.

A descriptive case series evaluated the effect of IGIV on quality of life in six adults with stiff person syndrome. Before and two weeks after a course of IGIV (400 mg/kg/day for five days), investigators assessed quality of life using the Short Form-36 (SF-36) and general health status by visual analog scale. Both general health status and total SF-36 score improved significantly with IGIV ($p<0.05$ vs. baseline for both outcomes). Subgroup analysis showed improvements in specific SF-36 subscales for pain, social functioning, mental health, and energy-vitality ($p<0.05$ vs. baseline for each subgroup). Five of six patients reported moderate-to-marked symptom improvement with IGIV.

- **Steroid-Resistant Dermatomyositis/Polymyositis:** Based on several clinical trials, IGIV improves functional ability, muscle strength, and nerve function. About 71–75% of patients reported improvement with IGIV therapy. Treatment with IGIV may be more effective in patients with shorter disease duration compared to those with longer disease duration. Dalakas et al. (1994) compared IGIV 2 g/kg IV monthly with placebo in patients with dermatomyositis refractory to prednisone or immunosuppressants. Patients were given three courses of therapy and then given the option of crossing over to the alternate therapy. Out of all patients treated, major functional improvement was reported more often with IGIV (75%) than placebo (0%, no statistics reported). Patients were less likely to report worsening function with IGIV (0%) than placebo (42%, no statistics reported). Mean number of muscle fibers decreased with IGIV, although mean fiber diameter increased significantly ($p<0.04$ vs. baseline). Mean number of muscle capillaries increased with IGIV, but mean capillary diameter decreased ($p<0.01$ vs. baseline). The muscle fiber to capillary ratio was 1.5 after IGIV treatment, approaching normal. Results were analyzed

both by original treatment allocation and separately in patients who chose to cross over. Four patients from each group chose to cross over to the alternate therapy. Results from the original treatment allocation showed that muscle strength improved with IGIV and was unchanged with placebo ($p < 0.018$ between groups). Similarly, mean neuromuscular symptom score improved from baseline with IGIV and was unchanged with placebo ($p < 0.035$ between groups). The greatest benefit of IGIV was seen in patients with the most severe weakness at baseline. After crossover, both muscle strength and neuromuscular symptoms improved in patients switching to IGIV but worsened in those switching to placebo (no statistics reported). A subgroup analysis of this trial evaluated the effects of IGIV on complement activation. Activated complement (C3) uptake was significantly inhibited with IGIV ($p < 0.001$ vs. baseline) but was unchanged with placebo (NS vs. baseline, not compared with IGIV). In patients given IGIV, complement membrane attack complexes were found in muscle capillaries prior to therapy, but completely disappeared after therapy. Results were not reported for the placebo group.

Few published trials have evaluated the efficacy of IGIV in patients with polymyositis. In a case series of 35 adults treated with polymyositis refractory to prednisone, immunosuppressants, pheresis, or radiotherapy, patients were treated for at least three months with IGIV 1 g/kg/day IV for two days each month. After IGIV treatment, muscle strength improved in 71% of patients, was unchanged in 26%, and worsened in 3%. Muscle disability score improved from baseline with IGIV ($p < 0.01$ vs. baseline). In patients with esophageal disorders at baseline, 73% reported resolution with IGIV. Mean disease duration was significantly shorter in patients responding to therapy (26 months) than in non-responders (43 months, $p < 0.05$ vs. responders). Creatine kinase decreased significantly with IGIV in responders ($p < 0.05$ vs. baseline) but was unchanged in non-responders. Daily steroid requirements were reduced significantly with IGIV (21.9 mg/day) compared to baseline (32.7 mg/day, $p < 0.05$ vs. baseline). Long-term efficacy was evaluated in 25 responders who were followed for a mean of 51.4 months. Forty-eight percent (12/25) of responders required no further therapy, while 24% (6/25) needed to continue IGIV, and 28% (7/25) relapsed. The mean time to relapse was 17.1 months after discontinuing IGIV therapy.

- **Toxic Shock Syndrome:** One placebo-controlled trial has evaluated IGIV (1 g/kg IV on day 1, then 500 mg/kg/day on days 2 and 3) in 21 patients with streptococcal toxic shock syndrome. Enrollment was terminated early due to slow patient recruitment, which may have reduced the study's power to detect treatment differences. Fewer patients had died at day 28 with IGIV (10%) than placebo (36%), although this did not reach statistical significance. Similar results were seen at day 120. Symptoms of shock resolved somewhat more quickly with IGIV (88 hours) than placebo (122 hours), although no statistics were reported for this comparison. However, it took longer for necrotizing fasciitis and cellulitis to stop progressing with IGIV (68 hours) than placebo (36 hours, no statistics reported). The sepsis-related organ failure score (or SOFA score) improved significantly more with IGIV at both days 2 and 3 than with placebo ($p < 0.05$ at both time points), and IGIV patients were more likely to have plasma neutralizing activity against superantigens ($p = 0.04$ vs. placebo).

The AHFS Drug Information[®] states that use of IGIV may be considered as an adjunct in the treatment of staphylococcal or streptococcal toxic shock syndrome. The American Academy of Pediatrics (AAP) states that IGIV may be considered in the management of staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the patient has persistent oliguria with pulmonary edema.

- **Hepatitis A Virus (HAV):** The Advisory Committee on Immunization Practices (ACIP) states that IGIV may be used as an alternative to IGIM for prophylaxis against HAV in patients with thrombocytopenia or disorders that cause IM hemorrhage and contraindicate use of IGIM. However, no data are available concerning the efficacy of IGIV in preventing HAV, and IGIM is the preferred preparation when immune globulin is indicated for prophylaxis of this infection. Because immune globulin modified for IV use is made from relatively small pools of donors, it may not contain antibodies to HAV.

- **Varicella:** IGIV has been used and is recommended as an alternative to VZIG for post-exposure prophylaxis of varicella infection in susceptible individuals when VZIG is unavailable. The ACIP states that VZIG is the preferred immune globulin for post-exposure prophylaxis of varicella in patients who do not have evidence of immunity (i.e., without a history of varicella or varicella vaccination) and are at high risk for severe disease and complications. When post-exposure prophylaxis of varicella is indicated, healthcare providers should make every effort to obtain and administer VZIG. However, when it does not appear possible to obtain VZIG within 96 hours of exposure, IGIV can be used as an alternative. The ACIP states that IGIV may be used in the following patients when VZIG is unavailable: immunocompromised patients, neonates whose mothers develop signs and symptoms of varicella around the time of delivery (i.e., five days before to two days after delivery), premature infants exposed during the neonatal period whose mothers do not have evidence of varicella immunity, or premature infants exposed during the neonatal period who were born at less than 28 weeks of gestation or with a birth weight of 1 kg or less (regardless of maternal history of varicella). In addition, the ACIP states that clinicians may choose to use IGIV for post-exposure prophylaxis of varicella in pregnant women. Post-exposure prophylaxis with IGIV may not be necessary in patients receiving IGIV replacement therapy (dosage of 400 mg/kg or greater given at regular intervals) if the last dose was administered within three weeks prior to exposure. Because post-exposure prophylaxis with IGIV may prolong the incubation period, patients who receive the immune globulin should be observed closely for signs or symptoms of varicella for 28 days following exposure. If the exposed patient does not develop varicella, varicella virus vaccine live should be administered at a later date, unless contraindicated.
- **Tetanus:** Although tetanus immune globulin (TIG) is the immune globulin of choice, IGIV can be used as an alternative for the treatment of tetanus when TIG is unavailable.
- **Immune Mediated Blistering Diseases:** Therapy with IGIV has been evaluated in many variants of immune mediated blistering diseases, primarily in case reports and case series. Clinical trials were included when available. The available evidence for each specific disorder is discussed in more detail below:
 - **Pemphigus Vulgaris:** Seven case series (n=62 total) discuss the effects of IGIV in resistant cases of pemphigus vulgaris. In two case series with similar methodology, patients received initial therapy with IGIV 1–2 g/kg IV divided and given over three days each cycle. This regimen was repeated every 3–4 weeks until all lesions were healed, then the cycle interval was gradually extended to 16 weeks before being discontinued. All 36 patients in these two reports experienced complete disease remission with this regimen. In three of the five remaining case series, IGIV 400 mg/kg/day IV for five days produced wound healing and disease remission in 18/19 patients. However, in the two remaining case series, clinical benefit was seen in only 1/10 patients, when given doses ranging from 400 mg/kg/day IV for five days to IGIV 2 g/kg IV every 3–4 weeks. Patients were able to reduce their corticosteroid requirements in two of the case series. The results of these seven case series are consistent with multiple single-case reports.
 - **Pemphigus Foliaceus:** Three case series (n=26 total) report the effects of IGIV in patients with pemphigus foliaceus. All three case series administered initial therapy with IGIV 1–2 g/kg IV divided and given over three days each cycle. This regimen was repeated every 3–4 weeks until all lesions were healed, then the cycle interval was gradually extended to 16 weeks before being discontinued. All 26 patients in the study responded to therapy, with 20/26 achieving complete remission and the others (6/26) experiencing clinical improvement. Corticosteroid requirements were significantly lower after IGIV therapy in two of the case series. These results are consistent with two additional case reports of single patients treated with 40–400 mg/kg/day for five days.
 - **Bullous Pemphigoid:** Six case series (n=35 total) report the effects of IGIV in bullous pemphigoid. Treatment with IGIV 2 g/kg (divided and given over 3–5 days) caused marked improvement in 28/33 patients, reducing appearance of new blisters, improving healing of old lesions, and reducing corticosteroid needs. Treatment was ineffective in

5/33 patients given this regimen after up to seven courses of therapy. In two patients given lower IGIV doses (100 or 300 mg/kg/day), no response occurred after the initial course, but both responded briefly to a second course of therapy. In many cases, relapse occurred within two weeks of the final IGIV dose, although some patients had more prolonged remissions.

- **Cicatricial Pemphigoid (or Mucus Membrane Pemphigoid):** There are no randomized clinical trials evaluating IGIV in patients with either the oral or ocular variants of this disorder. One observational follow-up study (n=20) and two case series (n=9) discuss the effects of IGIV in patients with oral-cicatricial pemphigoid. In the observational follow-up study, eight patients received initial therapy of IGIV 1–2 g/kg/cycle IV divided over three days. The cycle was repeated every four weeks until complete lesion healing, then the interval between cycles was gradually extended to 16 weeks before discontinuing therapy. Patients in the control group received conventional therapy with corticosteroids or immunosuppressants. Clinical remission was more common with IGIV (8/8, 100%) than conventional therapy (5/12, 42%, p<0.005). Clinical relapse was less common with IGIV (1/8, 13%) than conventional therapy (10/12, 83%, p<0.001). Two subsequent case series using similar IGIV regimens confirmed these results in nine patients with severe oral-cicatricial pemphigoid resistant to conventional therapy. One case report (n=1) found no benefit with IGIV, although no additional details are available.

In ocular-cicatricial pemphigoid, one observational follow-up study (n=16) and one case series (n=10) discuss the effects of IGIV in these patients. In the observational follow-up study, eight patients received initial therapy with IGIV 2 g/kg IV divided over three days. This cycle was repeated every two weeks until conjunctival inflammation resolved, then the interval between cycles was gradually extended to 16 weeks before discontinuing therapy. Patients in the control group received conventional therapy with immunosuppressives and as-needed corticosteroids. Clinical remission occurred in all 16 patients, although time to remission was significantly shorter with IGIV (four months) than conventional therapy (8.5 months, p<0.01). Ocular inflammation recurred more often with conventional therapy (5/8) than IGIV (0/8, p<0.05). Disease progression was more common with conventional therapy (4/8) than IGIV (0/8, p value not reported). These results were confirmed in a case series using a similar IGIV regimen in 10 patients with ocular-cicatricial pemphigoid resistant to conventional therapy. Similar results were also reported in two single-case reports.

- **Epidermolysis Bullosa Acquisita:** Eight case reports discuss the use of IGIV for this indication. These reports describe a total of eight patients (age 16–63 years) with a long duration (0.5–15 years) of refractory blistering and ulceration. In six out of eight reports, patients received IGIV 1.2–2 g/kg divided over 3–5 days, with cycles repeated every 2–6 weeks. This IGIV regimen produced dramatic resolution of blistering symptoms in all six patients. Similar results were noted with IGIV 40 mg/kg/day for five days in another case report, suggesting that lower doses may be effective in some patients. In one of the remaining reports, a patient received IGIV 2 g/kg/day every two weeks, but had no objective reduction in blistering after eight courses of therapy and three months of follow-up.

Unlabeled indications NOT included in criteria – Due to limited or insufficient clinical evidence, the use of IGIV for the following indications is not included in the criteria for the coverage policy.

- **Amyotrophic Lateral Sclerosis:** There are no published controlled trials evaluating IGIV in patients with amyotrophic lateral sclerosis (ALS). Two case series found that IGIV did not alter disease progression in patients treated for up to 13 months. In fact, disease symptoms continued to worsen during IGIV treatment, including muscle strength, disability, and bulbar function. In one case series, five of nine patients reported transient subjective improvements in muscle strength after the second IGIV dose. One study evaluated IGIV 1 g/kg/day for two days each month, while

the other evaluated IGIV 400 mg/kg/day IV for five days the first month followed by 400 mg/kg/day for two days each month thereafter.

- **Intractable Pediatric Epilepsy:** Immune globulin intravenous has been studied in many rare subtypes of pediatric epilepsy, including Landau-Kleffner syndrome, West syndrome, Rasmussen's syndrome, and Lennox-Gastaut syndrome. However, only two controlled trials have been published evaluating efficacy in refractory cases of these disorders. Based on these studies, IGIV may reduce seizure frequency more than placebo, although more study is needed.

Van Rijckevorsel-Harmant et al. (1994) found a trend toward more responders (patients with at least 50% decrease in seizure frequency) with IGIV (52%) than placebo (28%, $p=0.095$) for the entire study group. In the subgroup of patients with only partial seizures, response rate was higher with IGIV (56%) than placebo (17%, $p=0.041$). There was no relationship between IGIV dose and efficacy, although the study gave IGIV doses ranging from 100–400 mg/kg/dose given four times during the first week, then once weekly during weeks two, three and six. In the second study, IGIV 400 mg/kg IV given every 14 days reduced seizure frequency by 19–100% in 7/10 patients compared to placebo, although seizure frequency was unchanged in one patient and increased by 50–100% in the last two patients. There was marked variability between patients in type and frequency of seizures at baseline, and no comparative statistics were reported.

- **Autoimmune Neutropenia:** There are no published clinical trials of IGIV in patients with autoimmune neutropenia. Four case reports and four case series evaluated the effects of IGIV in this disorder. These reports describe a total of 21 patients (age range: one week to 67 years) with absolute neutrophil counts (ANC) less than 500 cells/mm³. Patients received regimens of IGIV 300–500 mg/kg/day for 2–6 days, IGIV 1 g/kg/day for two days, IGIV 1 g/kg/day until ANC is above 1,000 cells/mm³. In 19/21 patients, the initial course of IGIV increased ANC by 1,000–3,000 cells/mm³ from baseline. All 19 cases were reported as positive clinical responses to therapy. In two case series (13 patients), ANC returned to baseline an average of 14 days after IGIV therapy. In three reports (four patients), patients were given a second course of IGIV therapy after their ANC returned to baseline values. Only one of these patients experienced a meaningful increase in ANC after the second course of IGIV.
- **Immune Mediated Blistering Diseases:** Therapy with IGIV has been evaluated in many variants of immune mediated blistering diseases, primarily in case reports and case series. Clinical trials were included when available. The available evidence for each specific disorder is discussed in more detail below.
 - **Paraneoplastic Pemphigus:** Four case reports discuss the use of IGIV in paraneoplastic pemphigus. Therapy with IGIV was limited to a single dose in two reports and a single course of therapy in one report. The final report did not specify the IGIV dose or duration of therapy. Two patients improved slightly after IGIV, and one patient had no response. Therapy outcome was not reported for the final patient. There were many confounding factors in these reports, including use of multiple immunosuppressive agents and poor reporting. The clinical effects of IGIV remain unknown in this disorder.
 - **Pemphigoid Gestationis:** This related disorder has been evaluated only in single case reports (total of two patients), which are not included in the evidence tables. Patients were treated with 1–2 g/kg/day each month with good results. Both patients were able to reduce their corticosteroid requirements after IGIV therapy.
 - **Linear Immunoglobulin A (IgA) Bullous Disease.** Four case reports have evaluated IGIV in linear IgA bullous disease. Symptoms decreased in all patients after IGIV doses of 1–2 g/kg (given over 1–5 days), with courses repeated every 2–4 weeks. Response is maintained with continued therapy, although symptoms may recur within four weeks of the final dose.
 - **Stevens-Johnson Syndrome (Bullous Erythema Multiforme) / Toxic Epidermal Necrolysis:** The available literature discusses these two disorders interchangeably, and

most reports included patients with either disorder. Seven case series (n=136 total) and one observational follow-up study (n=11) report the effects of IGIV in these disorders. Patients received a wide range of IGIV doses, from 200 mg/kg/day to 2.9 g/kg/day, given for 1–5 days. In the observational follow-up study, IGIV did not significantly reduce fever duration or hospital length of stay, although favorable trends were noted for each outcome. Two case series compared actual mortality rates for patients given IGIV therapy to those predicted by the SCORTEN prognosis scale. Bachot et al. (2003) reported a higher actual mortality rate in patients given IGIV (32%) than the predicted mortality rate (21%), although the difference did not reach statistical significance. Most of the excess mortality occurred in patients over age 70; actual rate after IGIV 88%, predicted rate 38% (p=0.12). Trent et al. (2003) reported an actual mortality rate of 6% with IGIV compared to a predicted rate of 36%. Patients in this report suffered more extensive epidermal detachment and received twice as many days of IGIV therapy as those described by Bachot et al. (2003). In the five remaining case series, IGIV successfully interrupted epidermal necrolysis in 79/86 cases. These results are consistent with several single-case reports.

- **Primary Recurrent Spontaneous Miscarriage:** Seven randomized clinical trials and two meta-analyses have evaluated IGIV in women with recurrent spontaneous miscarriage. A variety of IGIV regimens were used including: 500 mg/kg monthly; 800 mg/kg weekly until 20 weeks gestation, then 1 g/kg every 14 days from 20–26 weeks gestation; 20 g every three weeks for five doses; 25 g/day for two days, then 25 g every three weeks; 30 g as a single dose, followed by 20 g every three weeks; or 30–40 g weekly in gestational weeks 5–6, followed by 20–30 g every 14 days in weeks 7–26, then 25–35 g every 14 days in weeks 28–34. It remains controversial whether IGIV improves live birth rates in these patients. The earliest randomized trial reported significantly higher live birth rates with IGIV (62%) than placebo (34%, p=0.04). However, the next six published trials found no benefit with IGIV, with live birth rates of 45–77% for IGIV and 29–79% for placebo. A 1998 meta-analysis of the first four trials found similar results. Live birth rate was 58% with IGIV and 48% with placebo (p=0.17). When patients with any other cause for miscarriage were excluded, live birth rate was higher with IGIV (63%) than placebo (49%, p=0.041). However, a 2003 Cochrane systematic review of all seven randomized trials found no difference in live birth rate between IGIV (58%) or placebo (59%). A 2006 Cochrane systematic review found similar results and concluded that IGIV provides no significant beneficial effect over placebo in improving the live birth rate. Case series and nonrandomized trials have been published but were not reviewed.
- **Secondary Recurrent Spontaneous Miscarriage:** A systematic search strategy was applied to Medline (1966 to June 2005) and the Cochrane Register of Controlled Trials (June 2005). Selection criteria included all randomized controlled trials comparing all dosages of IGIV to placebo or an active control. Two investigators independently extracted data using a standardized data collection form. Measures of effect were derived for each trial independently, and studies were pooled based on clinical and methodologic appropriateness. Eight trials were identified involving 442 women that evaluated IVIG therapy used to treat recurrent miscarriage. Overall, IGIV did not significantly increase the odds ratio (OR) of live birth when compared to placebo for treatment of recurrent miscarriage (OR 1.28, 95% CI 0.78-2.10). There was, however, a significant increase in live births following IGIV use in women with secondary recurrent miscarriage (OR 2.71, 95% CI 1.09–6.73), while those with primary miscarriage did not experience the same benefit (OR 0.66, 95% CI 0.35–1.26).

Immune globulin intravenous (human) is contraindicated in patients with selective IgA deficiency or prior anaphylactic reaction to IGIV. Patients with selective IgA deficiency have an increased risk of anaphylaxis to IGIV products containing IgA, even when only small concentrations are present. Select a product with lower IgA content (e.g., Gammagard, Polygam S/D) if IGIV treatment is necessary for such patients.

Immune globulin intravenous (human) has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. IGIV should be administered at the minimum concentration available and the minimum rate of infusion possible in patients who are predisposed to acute renal failure (e.g., patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65,

volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs). While renal dysfunction and acute renal failure have been reported with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

Patients with diabetes may be at risk for hyperglycemia when given IGIV products stabilized with glucose (e.g., Gammagard, Iveegam, Polygam S/D). Use of products without glucose may be warranted (Carimune NF, Flebogamma, Gamunex, Octagam).

Antibodies present in IGIV may interfere with the immune response to live viral vaccines, including measles, mumps, rubella, and varicella. These vaccines should not be administered simultaneously with or for specified intervals before or after administration of IGIV.

Adverse effects occur in 1–23% of patients given IGIV, but are usually mild. The most common reactions include fever, chills, rigors, tremor, flushing, renal dysfunction, headache, nausea, vomiting, diarrhea, back pain, chest pain, chest tightness, malaise, or myalgia. Many adverse effects are related to infusion rate and resolve when the infusion is slowed or temporarily stopped. Premedication with antihistamines, acetaminophen, or corticosteroids may prevent or alleviate these reactions.

Coding/Billing Information

Covered when medically necessary:

CPT [®] * Codes	Description
90283	Immune globulin (IgIV), human, for intravenous use
90399 [†]	Unlisted immune globulin
90779 [†]	Unlisted therapeutic, prophylactic or diagnostic intravenous or intra-arterial injection or infusion

HCPCS Codes	Description
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1567	Injection, immune globulin, intravenous, non-lyophilized (e.g. :powder), 500 mg (code deleted 01/01/08)
J1568	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma), intravenous, nonlyophilized (e.g., liquid), 500 mg
J7799 [†]	NOC drugs, other than inhalation solution, administered through DME
J3490 [†]	Unclassified drugs
J3590 [†]	Unclassified biologics
Q4082 [†]	Drug or biological, not otherwise classified, Part B drug competitive acquisition program (CAP)
Q4087	Injection, Immune Globulin (Octagam), Intravenous, non-lyophilized, (e.g.: liquid), 500 mg (code deleted 01/01/08-see J1568)
Q4088	Injection, Immune Globulin, (Gammagard), Intravenous, non-lyophilized (e.g. :liquid) 500 mg (code deleted 01/01/08-see J1569)
Q4091	Injection, Immune Globulin, (Flebogamma), Intravenous, non-lypphilized (e.g.:

	liquid) 500 mg (code deleted 01/01/08-see J1572)
Q4092	Injection, Immune Globulin, (Gamunex), Intravenous, non-lyophilized, (e.g. : liquid) 500 mg (code deleted 01/01/08-see J1561)
Q4097	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg (code deleted 1/1/09-see J1459)

†**Note: Covered when medically necessary when used to represent Immune Globulin Intravenous (Human, IGIV).**

The following ICD-9-CM Diagnosis Codes are covered when medically necessary subject to the criteria indicated in the Coverage Policy.

ICD-9-CM Diagnosis Codes	Description
037	Tetanus
040.82	Toxic shock syndrome
042	Human immunodeficiency virus [HIV]
052.0-052.9	Varicella
070.0	Viral hepatitis A with hepatic coma
070.1	Viral hepatitis A without mention of hepatic coma
079.83	Parvovirus B19
203.00	Multiple myeloma, without mention of having achieved remission
203.01	Multiple myeloma in remission
203.02	Multiple myeloma, in relapse
204.10	Chronic lymphoid leukemia, without mention of having achieved remission
204.11	Chronic lymphoid leukemia in remission
204.12	Chronic lymphoid leukemia, in relapse
279.00	Unspecified hypogammaglobulinemia
279.01	Selective IgA immunodeficiency
279.03	Other selective immunoglobulin deficiencies
279.04	Congenital hypogammaglobulinemia
279.05	Immunodeficiency with increased IgM
279.06	Common variable immunodeficiency
279.11	DiGeorge's syndrome
279.12	Wiskott-Aldrich syndrome
279.2	Combined immunity deficiency
283.0	Autoimmune hemolytic anemias
287.31	Immune thrombocytopenic purpura
287.32	Evans' syndrome
287.4	Secondary thrombocytopenia
333.91	Stiff-man syndrome
334.8	Other spinocerebellar diseases
340	Multiple sclerosis
357.0	Acute infective polyneuritis
357.81	Chronic inflammatory demyelinating polyneuritis
357.89	Other inflammatory and toxic neuropathy
358.01	Myasthenia gravis with (acute) exacerbation
358.1	Myasthenic syndromes in diseases classified elsewhere
359.89	Other myopathies
446.1	Acute febrile mucocutaneous lymph node syndrome (MCLS)
694.4	Pemphigus
694.5	Pemphigoid
694.60	Benign mucous membrane pemphigoid without mention of ocular involvement
694.61	Benign mucous membrane pemphigoid with ocular involvement
694.8	Other specified bullous dermatosis

710.3	Dermatomyositis
710.4	Polymyositis
773.0	Hemolytic disease due to Rh isoimmunization of fetus or newborn
773.1	Hemolytic disease due to ABO isoimmunization of fetus or newborn
773.2	Hemolytic disease due to other and unspecified isoimmunization of fetus or newborn
776.1	Transient neonatal thrombocytopenia
V42.81	Bone marrow replaced by transplant

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
138	Late effects of acute poliomyelitis
273.1	Monoclonal paraproteinemia
288.09	Other neutropenia
335.20	Amyotrophic lateral sclerosis
345.81	Other forms of epilepsy and recurrent seizures, with intractable epilepsy
356.4	Idiopathic progressive polyneuropathy
356.8	Other specified idiopathic peripheral neuropathy
356.9	Unspecified hereditary and idiopathic peripheral neuropathy
390	Rheumatic fever without mention of heart involvement
691.8	Other atopic dermatitis and related conditions
695.13	Stevens-Johnson syndrome
695.14	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
695.15	Toxic epidermal necrolysis
710.0	Systemic lupus erythematosus
728.89	Other disorder of muscle, ligament, and fascia
780.71	Chronic fatigue syndrome

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare (Human) (IGIV)	8/15/2008	5026	Immune Globulin Intravenous
Great-West Healthcare	12/2007	P02.104.2	Immune Globulins

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.