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DRUG USE EVALUATION: OFF-LABEL USE OF IMMUNE GLOBULIN G

The Immunoglobulin G (IgG) drug class evidence review on products identified strong evidence to support the use of intravenous and subcutaneous IgG for primary immunodeficiency and little evidence preferring one route over the other.[1] The goal of this evaluation is to define the appropriate off-label uses for IgG products and to assess Oregon Health Plan fee-for-service (OHP FFS) patients for appropriate use based on diagnosis and dosing with the available data.

Background:

Replacement IgG is approved by the US Food and Drug Administration (FDA) for treatment of primary humoral immunodeficiency (i.e. common variable immunodeficiency), multifocal motor neuropathy, beta-cell chronic lymphocytic leukemia, immune thrombocytopenic purpura, Kawasaki syndrome, and chronic inflammatory demyelinating polyneuropathy.[2] Primary immunodeficiency diseases are a group of greater than 150 genetically determined conditions including those which are caused by defects in antibody production, cellular or combined defects, phagocytic cell immune defects, and complement defects; all of which may result in recurrent or unusual infections.[3] There are also many off-label indications with evidence and guidelines supporting the use of IgG.[4]

Good quality, evidence-based Australian (2012)[5] and British (2008)[6] guidelines are published and generally similar in recommendations. The Australian guidelines (Appendix 1) determine whether a condition has an established therapeutic role or an emerging therapeutic role for IgG, whether IgG should be used in exceptional circumstances only or whether IgG use is not supported.[5] Australian guidelines recommend additional qualifying criteria for IgG treatment for inflammatory myopathies, for hypogammaglobulinemia secondary to hematopoietic stem cell transplant and for complications of renal transplantation.[5] Despite there being only small case studies to support IgG use in prevention or treatment of fetal or neonatal thrombocytopenia or hemorrhage, the Australian guidelines recommend use with qualifying criteria.[5] The British guidelines (Appendix 2) categorize IgG appropriateness as: yes (appropriate in all cases), selected (appropriate in selected cases with treatment priority defined as high, moderate, or low) and no (not appropriate).[6] The guidelines agree that amyotrophic lateral sclerosis, asthma, autism, recurrent spontaneous pregnancy loss, rheumatoid arthritis, and sepsis are conditions for which treatment with IgG is not supported or appropriate. Each guideline also exclusively lists various other conditions in this category.

A 2005 position statement on the appropriate use of IgG by the American Academy of Allergy Asthma & Immunology (AAAAI) recommends treatment in the following non-FDA approved conditions: Guillain-Barré syndrome, solid organ transplant recipients who experience acute rejection or who are HLA-sensitized for acute rejection, and toxic epidermal necrolysis/Stevens-Johnson syndrome.[7] The statement also mentioned conditions for which they could not make a recommendation, did not recommend, or conditions for which there is some data supporting IgG treatment. The criteria are summarized in Appendix 3.

Table 1 summarizes the agreement among these four sources. All FDA approved indications, Australian "established role" indications and British "yes" indications are included. AAAAI, Australian "emerging" and British "selected-high priority" indications were included if it was in agreement with the aforementioned group. There is a large grey area where the evidence supporting use of IgG in selected conditions is interpreted differently. Therefore, a case by case assessment of appropriateness may need to be done.

The recommended dose for each indication varies considerably (Table 1). Idaho Medicaid reported at a recent Drug Effectiveness Review Project meeting they realized a 25% cost avoidance from a single patient's therapy by correcting the dose for an obese patient to the recommended adjusted body weight rather than the actual body weight. Adjusted body weight is recommended by the British guidelines based upon two small studies.[8] Additionally, their review found a billing error where an office billed for immune globulin (brand name Privigen) 500mg as a single dose for four separate patients. The patients had actually received promethazine 50mg injectable.

Methods:

Patients with paid fee-for-service drug or professional claims for IgG from January 1, 2013 to December 31, 2013 were identified using the identifiers in Appendex 4. A claims summary of drug and professional claims for the last 13 months was reviewed for potential IgG indications. There were no minimum eligibility requirements or exclusions applied. Each patient was exclusively categorized in priority as: FDA approved diagnosis, evidence-supported off-label use, or unsupported off-label use.

In a subset of Oregon Health & Science University (OHSU) patients, the diagnosis, prescribed dose and weight was collected from the patient chart. This information was used to verify and supplement the claims diagnostic information and to verify dosing.

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TABLE 1. SUMMARY OF RECOMMENDED IGG INDICATIONS FROM FDA,[2] AUSTRALIA,[5] BRITAIN,[6] AND AAAAI[7]

Indications	Dose from MicroMedex or AHFS	FDA	AAAAI	Australian "Established Role"	Australian "Emerging Role"	British "Yes"	British "Selected - HIGH"	Agreement Score*
Primary humoral immunodeficiency (i.e. common variable immunodeficiency)	200 - 800 mg/kg IV infusion once every 3 to 4 week	1	1	1		1		4
immune thrombocytopenic purpura (ITP)	400 – 1000mg/kg IV QD x2-5 days	1	1	1			1	4
Kawasaki syndrome	2000mg/kg x1 or 400mg/kg QD x 4 days	1	1	1		1		4
chronic inflammatory demyelinating polyneuropathy	1000mg/kg every 3 weeks	1	1	1			1	4
Acquired hypogammaglobulinemia secondary to hematological malignancies (including beta-cell chronic lymphocytic leukemia)	400mg/kg every 3-4 weeks.	1	1	1		1		4
multifocal motor neuropathy	500-2500mg/kg every 4 weeks	1	1	1				3
Guillan-Barré syndrome	400mg/kg QD x 5 days		1	1			1	3
toxic epidermal necrolysis/Stevens-Johnson syndrome			1		1	1		3
solid organ transplantation	IVIg with plasma exchange: 0.1 to 0.5 g/kg IVIg alone: 2 g/kg to a maximum of 140 g as a single dose, or 2 to 3.5 g/kg in a divided dose.*		1		1			2
inflammatory myopathies (dermatomyositis, polymyositis, inclusion body myositis)				1			1	2
feto-maternal/neonatal alloimmune thrombocytopenia					1	1		2
IgM paraproteinemic neuropathy					1		1	2
myasthenia gravis				1				1
neonatal hemochromatosis				1				1
stiff person syndrome				1				1
Lambert-Eaton myasthenic syndrome				1				1
pneumonitis induced by cytomegalovirus following transplantation						1		1

*A "1" indicates the organization listed the diagnosis. These were summed across the row to determine agreement. A "4" indicates total agreement with FDA, AAAAI, Australia and British guidelines. *Dose for kidney transplant rejection provided by Australian guidelines*

Results:

There were 33 IgG patients identified. The majority of patients were female (67%) and over the age of 18 (85%). Eight patients were being managed by OHSU. Table 2 summarizes the patient demographics. During 2013, OHP FFS reimbursed $328,872 for IgG for these patients. Table 3 summarizes the distribution of products used.

Without scrutiny of the specific approved indications for each individual product, 24 (73%) patients had an FDA-approved diagnosis. A summary of these results, using the most applicable diagnosis of record for each individual, are in Table 3.

TABLE 2: PATIENT DEMOGRAPHICS

Demographic	**n = 33**	**%**
Female	22	67%
≤18 years old	5	15%
Mean Age (range)	41 (2-77)	N/A
Managing Facility Distribution		
OHSU	8	24%
Providence	6	18%
PeaceHealth	5	15%
Legacy Good Samaritan	2	6%
Mid Valley Healthcare	2	6%
Hematology Oncology of Salem	2	6%
Legacy Emanuel	1	3%
St. Charles	1	3%
Allergy and Asthma Center	1	3%
Saint Alphonsus	1	3%
Asante Three Rivers	1	3%
Grande Ronde	1	3%
Albany General	1	3%
Northwest Cancer Specialists	1	3%

TABLE 3. IgG PRODUCT UTILIZATION SUMMARY

Code	Descriptions	Patient Count	Claim Count	Paid Amount	Other Ins	Market Share by Paid Amount
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg	9	53	$123,633	$0	38%
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg	12	43	$80,447	$0	24%
NDC	HIZENTRA	2	20	$69,311	$15,426	21%
J1569	Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg	8	22	$30,907	$0	9%
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)	1	3	$9,598	$0	3%
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg	3	9	$6,541	$0	2%
J1561	Injection, immune globulin, (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg	2	12	$5,963	$0	2%
NDC	GAMMAGARD LIQUID	1	2	$1,814	$6,585	1%
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liguid), 500 mg	1	2	$656	$0	0%
	Unique Totals:	**33**	**166**	**$328,872**	**$22,012**	

Table 3: Diagnoses for patient claims.

Diagnostic Category	n=33	%
FDA approved diagnosis	**24**	**73%**
27906 Common Variable Immunodeficiency	9	27%
28731 Immune Thrombocytopenic Purpura	5	15%
35781 Chronic inflammatory demyelinating polyneuritis	3	9%
27903 Other selective immunoglobulin deficiencies	3	9%
27900 Hypogammaglobulinemia	3	9%
4461 Acute febrile mucocutaneous lymph node syndrome (Kawasaki Disease)	1	3%
Evidence-supported off-label diagnosis	**8**	**24%**
7103 Dermatomyositis	2	6%
7104 Polymyositis	1	3%
99681 Complications of transplanted kidney	3	9%
99688 Complications of transplanted organ, stem cell	1	3%
67803 Fetal hematologic conditions, antepartum condition or complication	1	3%
Other off-label diagnosis	**1**	**3%**
7100 Systemic lupus erythematosus	1	3%

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Table 4 is a summary of the verification and dose of the OHSU patients. Seven of the patients used Gammagard Liquid and one used Gamunex-C / Gammaked. Two patients are potentially not being dosed as recommended. Patient #5 has only received a single dose and the recommended dose is every 3-4 weeks. Patient #7 may need to be dosed with adjusted body weight.

TABLE 4 – SUMMARY OF OHSU ANALYSIS

Patient Number	Diagnosis	Weight (kg)	Height (in)	IBW (kg)	ABW (kg)	Prescribed Dose	Prescribed Freq	Calc max dose (g)	Appropriate dose?
1	Chronic inflammatory neuropathy, sarcoidosis	64.4	64.0	54.7	N/A	65 g (1 g/kg)	q3weeks	64	Y
2	Common Variable Immunodeficiency	73.2	68.5	69.6	N/A	25g (0.3/kg)	q2weeks	44	Y
3	Common Variable Immunodeficiency	49.9	61.0	52.4	N/A	40 g (0.8g/kg)	q4weeks?	40	Y
4	hypogammaglobulinemia, immunocompromised, graft vs. host disease (bone marrow)	59.6	73.0	79.9	N/A	10-30 g (0.2-0.5g/kg)	q4weeks	24	Y (deceased)
5	Common Variable Immunodeficiency	64.0	61.5	49.0	N/A	15 g (0.3 g/kg)	Once	38	N Dx unclear; If primary deficiency should be receiving q3-4 weeks
6	28731 Immune Thrombocytopenic Purpura	14.7	33.6	N/A	N/A	15 g (1g/kg)	Once	15	Y (ITP resolved)
7	Kidney transplant rejection	75.1	56.3	41.5	54.9	140 g (2 g/kg)	Once	110	N (Too high?)
8	Kidney transplant rejection	67.2	68.0	63.9	N/A	30 g (0.5 g/kg)	Once	34	Y

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Discussion:

Using a consensus of the FDA indications and AAAAI, Australian and British guidelines to indicate evidence supporting the use of IgG, 24 (73%) patients had a documented FDA-approved indication. Another 8 (24%) patients had documentation of an evidence supported indication. The claims analysis found 2 patients had diagnoses that needed further evaluation: Systemic lupus erythematosus and sarcoidosis.

Recommendations on thrombocytopenia secondary to sarcoidosis were not made in any of the guidelines.[5,6,7] Upon review, this particular patient's chart at OHSU indicated the patient also had chronic inflammatory neuropathy. The dosing schedule was consistent with a diagnosis of chronic inflammatory demyelinating polyneuropathy, an FDA-approved condition. The patient was re-categorized.

Thus, a single patient may have been prescribed IgG for a diagnosis with little evidence of benefit. Only a very small open-label trial consisting of 12 patients and scanty case reports are available to support the use of IgG in patients with systemic lupus erythematosus (SLE).[9] The Australian guidelines do not support use of IgG in patients with SLE due to preferable treatments being available.[5] It is possible this patient may have a qualifying diagnosis that was not included on claims to OHP FFS.

Two (25%) of the 8 OHSU patients were potentially dosed inappropriately. One patient with primary immunodeficiency received only 1 dose, whereas recommendations are to receive treatment every 3 to 4 weeks. It is possible this patient lost OHP FFS eligibility or died. Another apparently obese patient appeared to be dosed using the actual body weight rather than the adjusted body weight. This resulted an approximate 20% excessive dose (140 grams versus 110 grams).

There was some evidence of inappropriate use of IgG in OHP FFS in 2013. Given the high cost of IgG, any inappropriate use can be very costly. The mean cost per patient-year in 2013 was almost $10,000. However, development, maintenance and application of accurate drug use criteria in this rapidly changing and diverse field would be onerous.

Recommendations:

1) Perform a retrospective quarterly audit and report to P&T for all IgG claims to verify billing accuracy, evidence supported diagnosis and appropriate dosing.

References:

1. Fouts B. Abbreviated Class Review: Immunoglobulin G. 2014.

2. Immune Globulin Intravenous (IGIV) Indications. *US Food Drug Adm*. 2013. Available at: http://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsblas/fractionatedplasmaproducts/ucm133691.htm. Accessed February 21, 2014.

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7. Orange JS, Ballow M, Berger M. Position statement on the appropriate use of intravenously administered immunoglobulin (IGIV). *AAAAI Position Pap Use IGIV*. 2005:1–29.

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9. Francioni C, Galeazzi M, Fioravanti A, Gelli R, Megale F, Marcolongo R. Long-term I.V. Ig treatment in systemic lupus erythematosus. *Clin Exp Rheumatol*. 1994;12(2):163-8.

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Appendix:

Appendix 1: Australian criteria for the clinical use of immunoglobulin.[5]

Recommendation	Conditions
Conditions for which IgG has an established therapeutic role	Acquired hypogammaglobulinemia secondary to hematological malignancies, chronic inflammatory demyelinating polyneuropathy, Guillan-Barré syndrome, idiopathic (autoimmune) thrombocytopenia purpura (ITP) in adults, inflammatory myopathies (dermatomyositis, polymyositis, inclusion body myositis), Kawasaki disease, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, myasthenia gravis, neonatal hemochromatosis, primary immunodeficiency diseases, stiff person syndrome
Conditions for which IgG has an emerging therapeutic role	Acute disseminated encephalomyelitis, ANCA-positive systemic necrotizing vasculitis, autoimmune hemolytic anemia, bullous pemphigoid, cicatricial pemphigoid, Evans syndrome-autoimmune hemolytic anemia with immune thrombocytopenia, feto-maternal/neonatal alloimmune thrombocytopenia, hemophagocytic syndrome, idiopathic (autoimmune) thrombocytopenia purpura (ITP) in children, IgM paraproteinemic neuropathy, kidney transplantation, multiple sclerosis, opsoclonus myoclonus ataxia, pemphigus foliaceus, pemphigus vulgaris, post-transfusion purpura, secondary hypogammaglobulinemia (including iatrogenic immunodeficiency), specific antibody deficiency (including IgG subclasses), toxic epidermal necrolysis/Stevens-Johnson syndrome, toxic shock syndrome
Conditions for which IgG use is supported in exceptional circumstances only	Acute leukemia in children, autoimmune congenital heart block, autoimmune neutropenia, autoimmune uveitis, catastrophic antiphospholipid syndrome, coagulation factor inhibitors, Devic disease, diabetic amyotrophy, epidermolysis bullosa acquisita, epilepsy, Graves ophthalmopathy, hemolytic disease of the newborn, hemolytic transfusion reaction, Hashimoto encephalopathy, HIV in children, limbic encephalitis (nonparaneoplastic), myocarditis in children, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, paraneoplastic syndromes (subacute sensory neuropathy, cerebellar degeneration, limbic encephalitis), potassium channel antibody-associated encephalopathy, pure red cell aplasia, pure white cell aplasia, pyoderma gangrenosum, Rasmussen syndrome, scleromysedema, Sjogren's syndrome, solid organ transplantation (other than kidney), Susac syndrome, systemic capillary leak syndrome
Conditions for which IgG use is not supported	Acute optic neuritis, acute rheumatic fever, adrenoleukodystrophy, amegakaryocytic thrombocytopenia, antiphospholipid syndrome (non-obstetric), aplastic anemia/pancytopenia, asthma, atopic dermatitis/eczema-adult, autism, autologous hemopoietic stem cell transplantation, Hehçet's disease, cardiac surgery with bypass-prophylaxis, congestive cardiac failure, Crohn's disease, Diamond Blackfan syndrome, female infertility, glomerulonephritis-IgA nephritis, hemolytic uremic syndrome, Henoch-Schonlein purpura, HIV/AIDS-adult, idiopathic dilated cardiomyopathy, linear IgA disease, lupus cerebritis, lupus nephritis, motor neuron disease/amyotrophic lateral sclerosis, myalgic encephalomyelitis, narcolepsy/cataplexy, nephrotic syndrome, obsessive compulsive disorders, polyneuropathy of critical illness, recurrent fetal loss (with or without antiphospholipid syndrome), rheumatoid arthritis, sepsis, sickle cell disease, systemic lupus erythematosus, ulcerative colitis

Appendix 2: British criteria for the clinical use of immunoglobulin.[6]

Recommendation	Conditions
Appropriate in all cases if the physician wants to prescribe it	Kawasaki disease, primary immunodeficiencies, alloimmune thrombocytopenia-fetal therapy (treatment to the mother), low serum IgG levels after hematopoietic stem cell transplant for malignancy, toxic epidermal necrolysis/Stevens-Johnson syndrome, pneumonitis induced by cytomegalovirus following transplantation
Appropriate in only selected cases and in these, only if the physician wants to prescribe it (high priority)	Alloimmune thrombocytopenia-neonatal therapy, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura-pediatric (<16 years), idiopathic thrombocytopenic purpura-adult, chronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome, paraprotein associated demyelinating neuropathy (IgG or IgA), alloimmune thrombocytopenia-neonatal therapy, idiopathic thrombocytopenic purpura-pediatric (<16 years), juvenile dermatomyositis, dermatomyositis
Appropriate in only selected cases and in these, only if the physician wants to prescribe it (moderate priority)	Impaired specific antibody production, acquired red cell aplasia caused by parvovirus B19, adult HIV associated thrombocytopenia, autoimmune (acquired) hemophilia, autoimmune hemolytic anemia, Avans' syndrome, hemolytic disease of the fetus and newborn (isoimmune hemolytic jaundice in neonates), hemophagocytic lymphohistiocytosis/hemophagocytic syndrome, post-transfusion purpura, chronic lymphocytic leukemia, multiple myeloma, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, myasthenia gravis, paraprotein associated demyelinating neuropathy (IgM), Rasmussen syndrome, stiff person syndrome, immunobullous diseases, fetal hydrops, hemolytic disease of the fetus and newborn (isoimmune hemolytic jaundice in neonates), toxin related infection in pediatric intensive care, necrotizing (associated with Panton Valentine leukocidin) staphylococcal sepsis, severe invasive group A streptococcal disease, severe or recurrent *Clostridium difficile* colitis, staphylococcal toxic shock syndrome
Low treatment priority due to weak evidence base	Secondary antibody deficiencies, acquired red cell aplasia not caused by parvovirus B19, acquired von Willebrand's disease, aplastic anemia or pancytopenia, autoimmune neutropenia, hemolytic uremic syndrome, post-exposure prophylaxis for viral infection if intramuscular injection is contraindicated or if hyperimmune immunoglobulins are not available, post-transfusion hyperhemolysis (usually in patients with sickle cell disease), graft versus host disease after allogeneic bone marrow transplant or hematopoietic stem cell transplant, infection after allogeneic bone marrow transplant or hematopoietic stem cell transplant, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS), acute disseminated encephalomyelitis, acute idiopathic dysautonomia, autoimmune diabetic proximal neuropathy, Bickerstaff's brain stem encephalitis, central nervous system vasculitis, cerebral infarction with antiphospholipid antibodies, intractable childhood epilepsy, neuromyotonia, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), polymyositis polyneuropathy organomegaly endocrinopathy, monoclonal gammopathy skin changes (POEMS), potassium channel antibody associated non-neoplastic limbic encephalitis, vasculitic neuropathy, atopic dermatitis or eczema, pyoderma gangrenosum, urticarial, intractable childhood epilepsy, juvenile systemic lupus erythematosus, other systemic vasculitides, systemic juvenile idiopathic arthritis, catastrophic antiphospholipid syndrome, polymyositis, systemic lupus erythematosus, systemic lupus erythematosus with secondary immunocytopenia, systemic vasculitides and antineutrophil cytoplasmic antibody disorders, acute antibody mediated rejection after solid organ transplantation
Not appropriate	Immunodeficiency secondary to pediatric HIV infection, autologous bone marrow transplant, adrenoleukodystrophy, Alzheimer's disease, amyotrophic lateral sclerosis, autism, chronic fatigue syndrome, critical illness neuropathy, inclusion body myositis, multiple sclerosis, rheumatoid arthritis, neonatal sepsis (prevention or treatment), sepsis in the intensive care unit not related to specific toxins or *Clostridium difficile*, asthma, autoimmune uveitis, Graves' ophthalmopathy, failure of in vitro fertilization, recurrent spontaneous pregnancy loss

Appendix 3: AAAAI Recommendations for the Appropriate use of IgG.[7]

Recommendation	Condition
Recommended	FDA approved: Primary immunodeficiencies; prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia; prevention of coronary artery aneurysm in Kawasaki disease; prevention of infections and graft versus host disease after bone marrow transplantation; reduction of serious bacterial infection in HIV-infected children; increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding Non-approved: post-transfusion purpura; Guillain-Barré syndrome; chronic inflammatory demyelinating polyneuropathy; multifocal motor neuropathy; solid organ transplant recipients who experience acute rejection or who are HLA-sensitized for acute rejection; toxic epidermal necrolysis/Stevens-Johnson syndrome
Statement of evidence of some benefit	B cell chronic lymphocytic leukemia; HIV infected children; autoimmune thrombocytopenia; autoimmune hemolytic anemia; Evans syndrome; acquired hemophilia; rheumatoid arthritis; antiphospholipid antibody syndrome-related recurrent spontaneous abortion, in vitro fertilization; anti-neutrophil cytoplasmic antibody disorders; systemic sclerosis/scleroderma; Still's disease; individuals with antibody deficiency who have asthma-like symptoms; myasthenia gravis; Lambert Eaton myasthenic syndrome; relapsing-remitting multiple sclerosis; patients undergoing allogenic transplantation; autoimmune cytopenias occurring post-transplant; established bacterial septic shock; group B streptococcal disease; meningoencephalitis caused by enteroviral infection, pneumonitis caused by CMV; RSV pneumonitis in immunodeficient patients; cystic fibrosis
Recommended only with reservations	Organ-related complications of systemic lupus erythematosus including nephritis, myocarditis, polyradiculopathy, and bone marrow suppression; Graves' opthalmopathy; autoimmune uveitis; autoimmune chronic active hepatitis; intractable childhood epilepsy syndromes; bullous pemphigoid or other autoimmune blistering disorders
Not recommended or unable to make recommendation	Sepsis beyond neonatal period; multiple trauma; post-operative wounds; inflammatory myopathies; polymysitis; dermatomyositis; inclusion body myositis; severe asthma; acute graft versus host disease; anemia caused by chronic erythrovirus B-19 infection; *Campylobacter jejuni*; pseudomembranous colitis caused by *Clostridium difficile*; suspected sepsis; CMV gastroenteritis; established bacterial pneumonia; urticarial; atopic dermatitis; psoriasis; autism; chronic fatigue syndrome; pediatric autoimmune neuropsychiatric disorders with associated streptococcal infection (PANDAS); acute myocarditis; carditis of acute rheumatic fever; recently diagnosed dilated cardiomyopathy; pregnancy in women who experience recurrent spontaneous abortion

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Appendix 4 – Drug Identifiers

ProcCode	Descriptions
90283	Immune Globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liguid), 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg
HSN	Generic Drug Name
025631	IMMUNE GLOB,GAM CAPRYLATE(IGG)
033220	IMMUNE GLOBULIN,G(IGG)/MALTOSE
004202	IMMUNE GLOBULIN,GAMMA(IGG)