Drug Use Research & Management Program
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Drug Use Evaluation: Immune Globulins

Plain Language Summary:

- Immune globulins (IgG) are medicines used to:
  - help fight infections in people with immune systems that do not work normally or
  - treat muscle weakness in conditions caused when the immune system attacks parts of the body.
- Over a 2 year period from January 2022 to December 2023, 100 people had fee-for-service Medicaid claims for immune globulins. Medicaid was the primary payer for 35 of these people. Medicaid as "primary payer" is when a person does not have another kind of insurance, such private insurance, that also helps to pay a for a medicine.
- About 69% of people had a condition that immune globulins have been approved to treat by the Food and Drug Administration (FDA).
- Almost half (44%) of people with an initial denied claim had a second claim for immune globulin that was paid for. People were more likely to have an initial denied claim if they filled the medicine at a pharmacy.
- We recommend requiring a prior authorization for pharmacy claims to support use for off-label, evidence-supported indications.

Research Questions:

- What proportion of members prescribed IgG have an FDA-approved diagnosis?
- Are there certain populations based on diagnosis or billing method who are more likely to have paid or denied claims for IgG?
- What proportion of members with an initial denied claim have a subsequent paid claim?
- What proportion of units on medical claims are associated with waste?

Conclusions:

- Of members with claims for IgG, 35% of people had fee-for-service (FFS) Medicaid as the primary payer. About 74% of members had claims billed through the medical benefit, most commonly at outpatient hospitals. All pharmacy claims were for non-preferred products and were initially denied. Medical claims were paid.
- The most common products prescribed included GAMMAGARD, GAMUNEX-C, OCTAGAM, and HIZENTRA. About 69% of people (n=24) had an FDA-approved diagnoses present in medical claims and 23% (n=8) had an off-label diagnosis with some evidence for use. The most common FDA-approved diagnosis was primary immunodeficiency. The most common off-label diagnoses were pediatric acute-onset neuropsychiatric syndrome (PANS) or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and myasthenia gravis.
- Of the members with an initial denied pharmacy claim 78% (7 of 9) had an FDA-approved diagnosis present in medical claims. Four of these members had a subsequent paid claim for IgG in the next 3 months. Five members had no subsequent FFS claims but moved into a CCO or had other primary insurance who might have paid for IgG.
- There was insufficient data based on medical claims to identify what proportion of units are associated with waste.

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October 2024

Recommendations:

- Implement PA criteria for non-preferred IgG agents through the pharmacy benefit to support off-label use of IgG for evidence supported diagnoses.

Background

Immune globulins are available in a variety of brand names (**Table 1**). The FDA-labeled indications vary although all have the same active ingredient. Prior reviews have found no evidence to suggest differences in efficacy between formulations.[1,2] Immune globulins are also commonly used off-label for a variety of neurologic and immunologic indications, despite a lack of high-quality evidence. There is low quality evidence for some off-label indications that suggest efficacy, but most off-label indications have not been extensively studied.[2,3] A previous analysis of FFS utilization conducted in 2020 identified an FDA-approved indication for about 56% of patients and off-label indications for 34% of people who had claims for IgG.[2] Ongoing monitoring of off-label utilization was recommended at the time.

Currently, the preferred drug list applies to pharmacy claims and non-preferred drugs require prior authorization. The PA criteria limits utilization to FDA-approved indications. Preferred drugs are available without prior authorization, and medical claims do not have to be reviewed for FDA approved indications.

The goal of this analysis is to evaluate utilization of IgG for off-label diagnosis and how differences in policy implementation for pharmacy and medical claims may affect utilization.

Table 1. FDA-approved indications for IgG[4]

Product	Route	Primary humoral immunodeficiency*	Idiopathic thrombocytopenic purpura (chronic immune thrombocytopenia);	Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Other
Asceniv	IV	x			
Bivigam	IV	x			
Carimune	IV	x	x		
Cutaquig	SC	x			
Cuvitru	SC	x			
Flebogamma Dif	IV	x			
Gamastan	IM				Viral infection (Hepatitis A, measles or rubeola, varicella, rubella). Limitation: not for Hepatitis B
Gammagard (S/D, Liquid)	IV, SC	x	S/D	Liquid	S/D: Kawasaki Syndrome, B-cell Chronic lymphocytic leukemia Liquid: Multifocal motor Neuropathy
Gammaked	SC	x	x	x	
Gammaplex	IV	x	x		
Gamunex-C	IV, SC	x	x	x	
Hizentra	SC	x		x	

Hyqvia	SC	x		x	
Octagam	IV	x	x		Dermatomyositis
Panzyga	IV	x	x	x	
Privigen	IV	x	x	x	
Xembify	SC	x			

Abbreviations: IV = intravenous; SC = subcutaneous.

*Primary humoral immunodeficiency includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies

Methods:

OHP members were identified for inclusion in this evaluation based on paid or denied pharmacy or medical claims for immunoglobulins over a 2 year evaluation window (from 1/1/22 to 12/31/23). The first paid or denied claim was identified as the index event (IE). Denied claims were included if they had error codes indicating prior authorization was required (i.e., error 3022: non-preferred drug, error 3000: units exceed authorized units on PA master file, or error 3003: PA is required) and did not have any error codes indicating billing errors (**Appendix 1**). For members with paid and denied claims on the same day, the IE was classified as paid. For each patient, the 2 months before the IE was used to define the baseline period (inclusive of the IE) and the 3 months after the IE was used to define the follow-up period (exclusive of the IE).

Inclusion Criteria:

- OHP members with paid or denied pharmacy or medical FFS claims for drugs in the Immunoglobulins PDL class from 1/1/22 to 12/31/23

Exclusion Criteria:

- Members with less than 75% continuous OHP eligibility in the baseline period
- Members with Medicare eligibility, primary insurance (e.g, third-party-liability), or a limited Medicaid drug benefit in the baseline or follow-up period. Members with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these members may be incomplete. Members were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug
	BMD	Oregon Health Plan with Limited Drug
	MED	Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND	Transplant package
	CWM	Citizenship Waived Emergency Medical
	SMF	Special Low-Income Medicare Beneficiary Only
	SMB	Special Low-Income Medicare Beneficiary Only

Outcomes

- Proportion of members with an FDA-approved indication, evidence-supported off-label indication present in claims data. Indications were identified based on diagnoses submitted on the IE, on claims for IgG in the follow-up period, or on medical claims in the baseline period.
- Proportion of members who had a subsequent paid claim in the follow-up period for IgG following a denied IE.

- Proportion of units that were not administered to the member was defined based on modifier codes submitted with medical claims in the follow-up period. The amount of drug discarded was identified based on modifier code JW ("Discarded drug not administered") or modifier code JZ ("Zero drug wasted"). Medical codes can be submitted with either NDC units or procedure code units; procedure code units were used to describe utilization.

Results:

Over a 2 year period, 100 members had FFS claims for IgG (**Table 2**). Almost half of members (n=48) had Medicare or a limited drug benefit. Of the 52 remaining members, 17 (33%) had primary insurance. In total, 35 members with claims for IgG were included in the analysis where FFS Medicaid was the primary payer. Members were primarily adults (66%) and identified as white (63%; **Table 3**). The most common products prescribed included GAMMAGARD, GAMUNEX-C, OCTAGAM, and HIZENTRA. About 74% of members had claims billed through the medical benefit, most commonly at outpatient hospitals (**Table 3**). Twenty-six percent of members had claims billed through the pharmacy benefit. All pharmacy claims were initially denied and medical claims were paid (**Table 4**).

In the 9 members with initial denied pharmacy claims, 4 members had a subsequent paid claim for IgG in the next 3 months (**Table 7**). In the 5 members without a subsequent claim, 3 members were enrolled in a CCO and 2 members had other primary insurance coverage who might have paid for IgG.

In the 2 months before or 3 months after the IE, 69% of people (n=24) had an FDA-approved diagnoses present in medical claims, 23% (n=8) had an off-label diagnosis with some evidence for use (**Table 5**). Three members (9%) had a diagnosis that was not supported by evidence or unknown based on claims data. Of the members with an initial denied pharmacy claim 78% (7 of 9) had an FDA-approved diagnosis present in medical claims. The most common FDA-approved diagnoses were primary immunodeficiency, immune thrombocytopenia purpura, and chronic inflammatory demyelinating polyneuropathy (**Table 6**). The most common off-label diagnoses were PANS/PANDAS and myasthenia gravis or mononeuronal disorders.

Less than 10% of units billed on FFS medical claims were billed with modifiers to indicate how much drug was discarded or administered to the patient which significantly limits any analysis for waste (**Table 8**). About 44% of claims were billed with more than one size of vial which may indicate the provider was selecting products to minimize waste.

Table 2. Included members

	Total		Pharmacy		Medical	
	#	%	#	%	#	%
Members with a FFS paid or denied pharmacy or medical claim for IgG	100		19		81	
After exclusion of members with Medicare/limited drug benefit	52	52.0%	17	89.5%	35	43.2%
After exclusion of members with TPL and primary insurance payment > $0 on the IE	35	35.0%	9	47.4%	26	32.1%
After exclusion of members with <75% Medicaid enrollment in the baseline period	35	35.0%	9	47.4%	26	32.1%

Table 3. Demographics.

	Total Members	
Total	**35**	**%**
Average Age (min-max)	29	(1-61)
0-17	12	34.3%

>=18	23	65.7%
Gender		
Male	15	42.9%
Female	20	57.1%
Race		
White	22	62.9%
Unknown	5	14.3%
Other	8	22.9%
IgG Product		
GAMMAGARD LIQUID	14	40.0%
GAMUNEX-C	8	22.9%
OCTAGAM	5	14.3%
HIZENTRA	4	11.4%
PRIVIGEN	2	5.7%
CUVITRU	2	5.7%
IE Claim Type		
Outpatient Medical (hospital)	19	54.3%
Professional Medical (clinic)	7	20.0%
Pharmacy	9	25.7%

Table 4. Billing route and initial claim status for IgG

	Total		Pharmacy		Medical	
	35	%	9	%	26	%
Paid IE	26	74.3%	0	0.0%	26	100.0%
Denied IE	9	25.7%	9	100.0%	0	0.0%

Table 5. Member with paid and denied claims based on indication

	Total IE		Paid IE		Denied IE	
Indication	35	%	26	%	9	%
FDA-approved	24	68.6%	17	65.4%	7	77.8%
Off-label	8	22.9%	8	30.8%	0	0.0%

Other/unknown	3	8.6%	1	3.8%	2	22.2%

Table 6. Indications for IgG

	Total Members	
	35	**%**
FDA-approved indication (ICD-10 codes)	24	68.6%
Primary immunodeficiency (D80x-D84x)	16	45.7%
Immune thrombocytopenia purpura (D693x)	4	11.4%
Chronic inflammatory demyelinating polyneuropathy (G6181)	3	8.6%
Dermatomyositis (M33x)	2	5.7%
B-cell chronic lymphocytic leukemia (C911x)	2	5.7%
Kawasaki disease (M303)	1	2.9%
Multifocal motor neuropathy (G6182)	0	0.0%
Off-label indications (ICD-10 codes)	8	22.9%
PANS/PANDAS (D8989, D899)	2	5.7%
Myasthenia gravis and myoneural disorders (G70x)	2	5.7%
Transplant complications/rejection (T86x, Z94x, Z482x)	1	2.9%
Pemphigus and pemphigoid (L10x, L12x)	1	2.9%
Encephalitis and encephalopathy (G04x)	1	2.9%
Stiff person syndrome (G2582)	1	2.9%
Scleroderma (L940, L941, M34x)	1	2.9%
Other inflammatory neuropathy (G611x, G6189, G619)	0	0.0%
Guillain-Barre syndrome (G610)	0	0.0%
Other thrombocytopenia (D694x-D696x, P610, O3682)	0	0.0%
Multiple sclerosis (G35x)	0	0.0%
Systemic lupus erythematosus (M32x)	0	0.0%
Myocarditis (A381, A3952, B2682, B3322, B5881, D8685, I012, I090, I40x, I41x, I514x, J1082, J1182)*	0	0.0%
Sjögren syndrome (M350x)	0	0.0%
Toxic epidermal necrolysis (TEN)/ Stevens-Johnson syndrome (SJS) (L511x-L513x)	0	0.0%
None of the above	3	8.6%
Top 10 other diagnoses billed on IgG claims	1	2.9%
G608 - Other hereditary and idiopathic neuropathies	1	2.9%
G629 - Polyneuropathy, unspecified	1	2.9%
G9009 - Other idiopathic peripheral autonomic neuropathy	1	2.9%

Table 7. Follow-up for members with denied pharmacy claims

Indication	Members with FDA approved indication		Members with Off-label/unknown indications	
	24	%	11	%
Total members with denied IE	7	29.2%	2	18.2%
Subsequent paid claim for IgG in the follow-up period	3	12.5%	1	9.1%
No subsequent paid claim for IgG	4	16.7%	1	9.1%
Enrolled in a CCO	3	12.5%	0	0.0%
Active other insurance (TPL)	1	4.2%	1	9.1%

Table 8. Amount of discarded drug for paid medical claims

	Claims*		Members*		Units	
	45	%	21	%	4,196	%
Drug discarded (JW)	3	3.4%	2	9.5%	30	0.7%
No drug wasted (JZ)	6	12.6%	2	9.5%	382	9.1%
Neither of the above	39	83.9%	19	90.5%	3784	90.2%

*May be duplicative as claims should be submitted with multiple lines to indicate amount of drug that was discarded or administered

Limitations/Discussion:

Inherent limitations to Medicaid claims data include:

- Diagnoses data based on claims may be inaccurate or incomplete. Diagnoses must be submitted for PAD claims, but are not associated with POS pharmacy claims; therefore, it is difficult to determine the intended indication of the drug.
- Most members with claims for IgG were excluded from the analysis because they had Medicare, a limited Medicaid drug benefit or other insurance. Only about one-third of members (35 people over 2 years) had claims for IgG where FFS Medicaid was the primary payer.
- Medical claims are not submitted with a days' supply and it is difficult to estimate duration of therapy based on medical utilization. We did not attempt to quantify number of claims or units of IgG dispensed per member or for each diagnosis. The follow-up period was limited to 3 months, and in that time 3 of the 9 members with denied claims had moved into a CCO.

References:

1. Drug Use Research and Management Program. Abbreviated Class Review: Immunoglobulin G. March 2014. https://www.orpdl.org/durm/meetings/meetingdocs/2014_03_27/archives/2014_03_27_ImmunoglobulinCR_V4.pdf. Accessed August 29, 2024.
2. Drug Use Research and Management Program. Drug Use Evaluation: Immune Globulins. August 2020. https://www.orpdl.org/durm/meetings/meetingdocs/2020_08_06/archives/2020_08_06_Immunoglobulin_DUE.pdf. Accessed August 29, 2024.
3. Immune Globulin In: Merative Micromedex® Alternative Medicine (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: August 29, 2024).
4. Food and Drug Administration. Immune Globulins. https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Updated March 8, 2023. Accessed July 1, 2024.

Appendix 1: Coding

Table A1. Error Codes indicating billing errors

Error Code	Description
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)
643	INVALID OTHER COVERAGE CODE
2509	RECIPIENT COVERED BY MEDICARE
576	CLAIM HAS THIRD-PARTY PAYMENT
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER
2504	RECIPIENT COVERD BY PRIVATE INSURANC(NO ATTACHMNT)
2505	RECIPIENT COVERED BY PRIVATE INSURANC(W/ATTACHMNT)

Appendix 2: Proposed Prior Authorization Criteria

Immunoglobulins

Goal(s):

- Ensure that medications for immunoglobulins are used appropriately for OHP-funded conditions.
- Provide coverage for off-label indications that have evidence for use.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred immunoglobulin

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved Indications and Off-label Immune Globulin Indications

FDA Approved Indications	Adults	Pediatrics
B-cell chronic lymphocytic leukemia variant (CLL)	Yes	No
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Yes	No
Dermatomyositis	Yes	No
Hepatitis A Prophylaxis	Yes	No

Idiopathic thrombocytopenic purpura (ITP)	Yes	Yes -2 years and up
Kawasaki Disease	No	Yes
Measles Prophylaxis and post-exposure prophylaxis	Yes	Yes
Multifocal motor neuropathy (MMN)	Yes	No
Primary humoral immunodeficiencies (PI)*	Yes	Yes - 2 years and up
Rubella in pregnancy	Yes	No
Varicella prophylaxis	Yes	No
Off-Label Indications with Evidence for Efficacy	**Adults**	**Pediatrics**
Autoimmune hemolytic anemia	Yes	No
Autoimmune necrotizing myopathy	Yes	No
Autoimmune neutropenia	Yes	No
Cytomegalovirus infection	Yes	No
Guillain-Barre syndrome	Yes	Yes
Human Immunodeficiency Virus (HIV)	No	Yes
IgA nephropathy	Yes	No
Multisystem inflammatory syndrome in children; associated with SARS-CoV-2	No	Yes
Myasthenia Gravis	Yes	No
Neonatal jaundice	No	Yes
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)	No	Yes
Pemphigus	Yes	No
Respiratory syncytial virus	No	Yes
Toxic shock syndrome	Yes	No
Transplant rejection or desensitization	Yes	No
Uveitis	Yes	No
Von Willebrand disorder	Yes	No

* Primary humoral immunodeficiency includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No**: Go to #3
3. Is the request for continuation of therapy previously approved by fee-for-service?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for an FDA-approved indication or for an off-label indication, with evidence of efficacy, listed in Table 1?	**Yes**: Approve for 6 months	**No:** Go to #5
5. Is the request for continuation after a hospital discharge?	**Yes:** Approve for 6 months	**No:** Go to #6
6. Is the medication prescribed by, or in consultation with a neurologist, transplant provider, infectious disease, or other relevant specialist for the requested condition?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for acute treatment anticipated to last less than 3 months?	**Yes:** Approve for requested duration	**No:** Go to #8
8. Is there objective documentation of disease severity using a validated measure? Examples could include number of hospitalizations, quality of life assessed using the Short-Form 36, clinical test results, or other symptom assessment scale relevant to the requested condition.	**Yes:** Go to #9 Document disease severity	**No:** Pass to RPh. Deny; medical appropriateness
9. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for conditions which are not outlined above is currently insufficient and should be denied for "medical appropriateness" If new evidence or guideline-recommendations are provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Renewal Criteria		
1. Is there documentation to demonstrate clinically meaningful improvement in symptoms, function, disease severity, or quality of life since initiation of treatment? The same clinical measure used to document disease severity is recommended to document clinical benefit.	**Yes:** Approve for 12 months	**No**: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 10/24 (KS)
Implementation: 12/1/2024