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PHARMACY / MEDICAL POLICY – 5.01.564

Pharmacotherapy of Miscellaneous Autoimmune Diseases

Effective Date:	July 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	June 11, 2024	5.01.550 Pharmacotherapy of Arthropathies
Replaces:	Extracted from 5.01.550	5.01.556 Rituximab: Non-oncologic and Miscellaneous Uses
		5.01.563 Pharmacotherapy of Inflammatory Bowel Disorder
		5.01.575 C5 Complement Inhibitors
		11.01.523 Site of Service: Infusion Drugs and Biologic Agents

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

The term "autoimmune disorders" refers to a number of conditions where a person's immune system is activated against a part of their body. Many of these diseases are grouped together based on what part of the body is affected. The cells involved are usually lymph cells, and disease develops consistent with long standing inflammation. Common autoimmune disorders include certain types of arthritis, some skin diseases, inflammatory bowel diseases and others. This policy discusses treatment for the following autoimmune diseases: hidradenitis suppurativa, systemic lupus erythematosus (lupus), pyoderma gangrenosum, Behcet's disease, giant cell arteritis, uveitis, neuromyelitis optica spectrum disorder, periodic fever syndromes, Still's disease, recurrent pericarditis, deficiency of interleukin-1 receptor antagonist, and primary immunoglobulin A nephropathy (IgAN). The policy describes which drugs need to be pre-approved before they are covered by the plan.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Avsola (infliximab-axxq)
- Benlysta (belimumab)
- Inflectra (infliximab-dyyb)
- Infliximab (Janssen – unbranded)
- Remicade (infliximab)
- Renflexis (infliximab-abda)
- Uplizna (inebilizumab-cdon)

Note: Medications listed in this policy may also be subjected to quantity limits per the FDA labeled dosing.

Click on the links below to be directed to the related medical necessity criteria:

Behcet's Disease

Cytokine Release Syndrome

Giant Cell Arteritis

Hidradenitis Suppurativa (HS)

Pyoderma Gangrenosum

Site of Service

Systemic Lupus Erythematosus (SLE) & Lupus Nephritis

Uveitis

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

Recurrent Pericarditis

Periodic Fever Syndromes & Still's Disease

Graft Versus Host Disease

Myasthenia Gravis

Primary Immunoglobulin A Nephropathy (IgAN)

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe, and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe, and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy*

Site of Service Administration	Medical Necessity
	Note: *This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:** • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Agent	Medical Necessity
Hidradenitis Suppurativa (HS)	
First-line TNF-α Antagonists	

Agent	Medical Necessity
• **Adalimumab-adaz (Hyrimoz unbranded) SC** • **Adalimumab-adbm (Cyltezo unbranded) SC** • **Adalimumab-ryvk (Simlandi unbranded) SC** • **Cyltezo (adalimumab-adbm) SC** • **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] SC** • **Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314] SC** • **Simlandi (adalimumab-ryvk) SC** **Managed under pharmacy benefit**	**Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314], and Simlandi (adalimumab-ryvk) may be considered medically necessary for the treatment of hidradenitis suppurativa when:** • Individual is ≥ 12 years of age **AND** • Individual has tried at least one other therapy (e.g., intralesional or oral corticosteroids, systemic antibiotics) **AND** • The medication is prescribed by or in consultation with a dermatologist
Second-line IL-17 Antagonists	
Cosentyx (secukinumab) SC **Managed under pharmacy benefit**	**Cosentyx (secukinumab) may be considered medically necessary for the treatment of hidradenitis suppurativa when:** • Individual is ≥ 18 years of age **AND** • Individual has tried at least one other therapy (e.g., intralesional or oral corticosteroids, systemic antibiotics) **AND** • The medication is prescribed by or in consultation with a dermatologist
Second-line TNF-α Antagonists	
• **Abrilada (adalimumab-afzb) SC** • **Adalimumab-aacf (Idacio unbranded) SC** • **Adalimumab-aaty (Yuflyma unbranded) SC** • **Adalimumab-fkjp (Hulio unbranded) SC**	**Abrilada (adalimumab-afzb), adalimumab-aacf (Idacio unbranded), adalimumab-aaty (Yuflyma unbranded), adalimumab – fkjp (Hulio unbranded), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Humira (adalimumab) (Cordavis) [NDCs starting with 83457], Hyrimoz (adalimumab-adaz) (Cordavis) [NDCs starting with 83457], Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty) and Yusimry**

Agent	Medical Necessity

• **Amjevita (adalimumab-atto) SC**
• **Hadlima (adalimumab-bwwd) SC**
• **Hulio (adalimumab-fkjp) SC**
• **Humira (adalimumab) (Cordavis) [NDCs starting with 83457] SC**
• **Hyrimoz (adalimumab-adaz) (Cordavis) [NDCs starting with 83457] SC**
• **Idacio (adalimumab-aacf) SC**
• **Yuflyma (adalimumab-aaty) SC**
• **Yusimry (adalimumab-aqvh) SC**
 	
Managed under pharmacy benefit
	(adalimumab-aqvh) may be considered medically necessary for the treatment of hidradenitis suppurativa when:
	• Individual is ≥ 12 years of age
	AND
	• Individual has tried at least one other therapy (e.g., intralesional or oral corticosteroids, systemic antibiotics)
	AND
	• Individual has had an inadequate response or intolerance to ALL the following agents:
	  ○ Cyltezo (adalimumab-adbm) OR adalimumab-adbm (Cyltezo unbranded)
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314] OR adalimumab-adaz (Hyrimoz unbranded)
	  ○ Simlandi (adalimumab-ryvk) OR adalimumab-ryvk (Simlandi unbranded)
	AND
	• The medication is prescribed by or in consultation with a dermatologist

Systemic Lupus Erythematosus (SLE) & Lupus Nephritis	
Anti-CD20 • **Rituxan (rituximab)** • **Ruxience (rituximab-pvvr)** • **Truxima (rituximab-abbs)**	**See policy 5.01.556 Rituximab: Non-oncologic and Miscellaneous Uses**
BLyS Inhibitors	
Benlysta (belimumab) IV **Managed under medical benefit**	**Benlysta (belimumab) IV is subject to review for site of service administration.** **Benlysta (belimumab) IV may be considered medically necessary for the treatment of active, autoantibody positive SLE when the following conditions are met:** • The individual is 5 years of age or older **AND** • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or
Benlysta (belimumab) SC **Managed under pharmacy and medical benefit**	

Agent	Medical Necessity
	Systemic Lupus International Collaborating Clinics (**SLICC**) criteria **AND** • Benlysta (belimumab) IV is being used as add-on-therapy following standard induction therapy with mycophenolate, cyclophosphamide, azathioprine, or immunosuppressant, plus a corticosteroid **AND** • Benlysta (belimumab) IV is not used concurrently with Saphnelo (anifrolumab-fnia) for the treatment of SLE **Benlysta (belimumab) SC may be considered medically necessary for the treatment of active, autoantibody positive SLE when the following conditions are met:** • The individual is 5 years of age or older **AND** • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or Systemic Lupus International Collaborating Clinics (**SLICC**) criteria **AND** • Benlysta (belimumab) SC is being used as add-on-therapy following standard induction therapy with mycophenolate, cyclophosphamide, azathioprine, or immunosuppressant, plus a corticosteroid **AND** • Benlysta (belimumab) SC is not used concurrently with Saphnelo (anifrolumab-fnia) for the treatment of SLE **Benlysta (belimumab) IV may be considered medically necessary for the treatment of pediatric and adult individuals with active lupus nephritis who are receiving standard therapy when the following conditions are met:** • The individual is 5 years of age or older **AND** • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or

Agent	Medical Necessity
	Systemic Lupus International Collaborating Clinics (**SLICC**) criteria **AND** • The individual is receiving standard therapy with mycophenolate, cyclophosphamide, azathioprine, or immunosuppressant, plus a corticosteroid **AND** • The individual has class III (focal proliferative), class IV (diffuse proliferative), and/or class V (membranous) lupus nephritis **AND** • No previous use of dialysis in the past 12 months **AND** • Benlysta (belimumab) is not used concurrently with Lupkynis (voclosporin) for the treatment of active lupus nephritis **AND** • Benlysta (belimumab) is prescribed by or in consultation with a nephrologist or rheumatologist **Benlysta (belimumab) SC may be considered medically necessary for the treatment of adult individuals with active lupus nephritis who are receiving standard therapy when the following conditions are met:** • The individual is 18 years of age or older **AND** • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or Systemic Lupus International Collaborating Clinics (**SLICC**) criteria **AND** • The individual is receiving standard therapy with mycophenolate, cyclophosphamide, azathioprine, or immunosuppressant, plus a corticosteroid **AND** • The individual has class III (focal proliferative), class IV (diffuse proliferative), and/or class V (membranous) lupus nephritis **AND**

Agent	Medical Necessity
	• No previous use of dialysis in the past 12 months **AND** • Benlysta (belimumab) is not used concurrently with Lupkynis (voclosporin) for the treatment of active lupus nephritis **AND** • Benlysta (belimumab) is prescribed by or in consultation with a nephrologist or rheumatologist
Calcineurin Inhibitors	
Calcineurin Inhibitor • **Lupkynis (voclosporin) oral** **Managed under pharmacy benefit**	**Lupkynis (voclosporin) may be considered medically necessary for the treatment of adult individuals with active lupus nephritis who are receiving standard therapy when the following conditions are met:** • The individual is 18 years of age or older **AND** • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or Systemic Lupus International Collaborating Clinics (**SLICC**) criteria **AND** • Lupkynis (voclosporin) will be used in combination with mycophenolate, cyclophosphamide, azathioprine, or an immunosuppressant AND a corticosteroid **AND** • The individual has class III (focal proliferative), class IV (diffuse proliferative), and/or class V (membranous) lupus nephritis **AND** • No previous use of dialysis in the past 12 months **AND** • Lupkynis (voclosporin) is not used concurrently with Benlysta (belimumab) for the treatment of active lupus nephritis **AND** • The dose prescribed is ≤ 47.4 mg per day (taken as three 7.9 mg capsules twice daily) **AND** • Lupkynis (voclosporin) is prescribed by or in consultation with a nephrologist or rheumatologist

Agent	Medical Necessity
Type I Interferon (IFN) Receptor Antagonist	
Type I IFN Receptor Antagonist • **Saphnelo (anifrolumab-fnia) IV** **Managed under medical benefit**	**Saphnelo (anifrolumab-fnia) may be considered medically necessary for the treatment of adult individuals with moderate to severe systemic lupus erythematosus (SLE) when the following conditions are met:** • The individual is 18 years of age or older **AND** • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or Systemic Lupus International Collaborating Clinics (**SLICC**) criteria **AND** • Saphnelo (anifrolumab-fnia) is being used as add-on therapy following standard induction therapy with mycophenolate, azathioprine, or immunosuppressant, plus a corticosteroid **AND** • The individual does not have severe (IV cyclophosphamide and/or high dose IV pulse corticosteroid is not used) active central nervous system lupus **AND** • The individual does not have severe (IV cyclophosphamide and/or high dose IV pulse corticosteroid is not used) active lupus nephritis **AND** • Saphnelo (anifrolumab-fnia) is not used concurrently with Benlysta (belimumab) for the treatment of SLE
Pyoderma Gangrenosum	
First-line Agents	
TNF-α Antagonists • **Adalimumab-adaz (Hyrimoz unbranded) SC** • **Adalimumab-adbm (Cyltezo unbranded) SC** • **Adalimumab-ryvk (Simlandi unbranded) SC** • **Cyltezo (adalimumab-adbm) SC**	**Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314], Simlandi (adalimumab-ryvk), and Enbrel (etanercept) may be considered medically necessary for the treatment of pyoderma gangrenosum when:**

Agent	Medical Necessity
• **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] SC** • **Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314] SC** • **Simlandi (adalimumab-ryvk) SC** • **Enbrel (etanercept) SC** **Managed under pharmacy benefit**	• The individual has not responded to one standard non-biologic therapy (e.g., oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.) **AND** • The medication is prescribed by or in consultation with a dermatologist
TNF-α Antagonists • **Avsola (infliximab-axxq) IV** • **Infliximab (Janssen – unbranded) IV** • **Remicade (infliximab) IV** **Managed under medical benefit**	**Avsola (infliximab-axxq), Infliximab (Janssen – unbranded), and Remicade (infliximab) are subject to review for site of service administration.** **Avsola (infliximab-axxq), Infliximab (Janssen – unbranded), and Remicade (infliximab) may be considered medically necessary for the treatment of pyoderma gangrenosum when:** • The individual has not responded to one standard non-biologic therapy (e.g., oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.) **AND** • The medication is prescribed by or in consultation with a dermatologist
Second-line Agents	
TNF- α Antagonists • **Renflexis (infliximab-abda) IV** • **Inflectra (infliximab-dyyb) IV** **Managed under medical benefit**	**Renflexis (infliximab-abda) and Inflectra (infliximab-dyyb) are subject to review for site of service administration.** **Renflexis (infliximab-abda) and Inflectra (infliximab-dyyb) may be considered medically necessary for the treatment of pyoderma gangrenosum when:** • The individual has not responded to one standard non-biologic therapy (e.g., oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.) **AND**

Agent	Medical Necessity
	• The individual has had an inadequate response or intolerance to Avsola (infliximab-axxq), Infliximab (Janssen – unbranded) or Remicade (infliximab) **AND** • The medication is prescribed by or in consultation with a dermatologist

TNF-α Antagonists
• **Abrilada (adalimumab-afzb) SC**
• **Adalimumab-aacf (Idacio unbranded) SC**
• **Adalimumab-aaty (Yuflyma unbranded) SC**
• **Adalimumab-fkjp (Hulio unbranded) SC**
• **Amjevita (adalimumab-atto) SC**
• **Hadlima (adalimumab-bwwd) SC**
• **Hulio (adalimumab-fkjp) SC**
• **Humira (adalimumab) (Cordavis) [NDCs starting with 83457] SC**
• **Hyrimoz (adalimumab-adaz) (Cordavis) [NDCs starting with 83457] SC**
• **Idacio (adalimumab-aacf) SC**
• **Yuflyma (adalimumab-aaty) SC**
• **Yusimry (adalimumab-aqvh) SC**
 	
Managed under pharmacy benefit
	Abrilada (adalimumab-afzb), adalimumab-aacf (Idacio unbranded), adalimumab-aaty (Yuflyma unbranded), adalimumab-fkjp (Hulio unbranded), Amjevita (adalimumab-atto), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Humira (adalimumab) (Cordavis) [NDCs starting with 83457], Hyrimoz (adalimumab-adaz) (Cordavis) [NDCs starting with 83457], Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty), and Yusimry (adalimumab-aqvh) considered medically necessary for the treatment of pyoderma gangrenosum when:
	• The individual has not responded to one standard non-biologic therapy (e.g., oral corticosteroids, systemic cyclosporine, topical tacrolimus, etc.)
	AND
	• Individual has had an inadequate response or intolerance to ALL the following agents:
	  ○ Cyltezo (adalimumab-adbm) OR adalimumab-adbm (Cyltezo unbranded)
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314] OR adalimumab-adaz (Hyrimoz unbranded)
	  ○ Simlandi (adalimumab-ryvk) OR adalimumab-ryvk (Simlandi unbranded)
	AND
	• The medication is prescribed by or in consultation with a dermatologist

Uveitis	
First-line Agents	

Agent	Medical Necessity

TNF-α Antagonists
• **Adalimumab-adaz (Hyrimoz unbranded) SC**
• **Adalimumab-adbm (Cyltezo unbranded) SC**
• **Adalimumab-ryvk (Simlandi unbranded) SC**
• **Cyltezo (adalimumab-adbm) SC**
• **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] SC**
• **Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314] SC**
• **Simlandi (adalimumab-ryvk) SC**
 	
Managed under pharmacy benefit
	Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314], and Simlandi (adalimumab-ryvk) may be considered medically necessary for the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis when:
	• Individual is ≥ 2 years of age
	AND
	• Individual has tried one of the following therapies:
	  ○ Periocular, intraocular, or systemic corticosteroids
	  ○ Immunosuppressives
	AND
	• The medication is prescribed by or in consultation with an ophthalmologist

Second-line Agents	

TNF-α Antagonists
• **Abrilada (adalimumab-afzb) SC**
• **Adalimumab-aacf (Idacio unbranded) SC**
• **Adalimumab-aaty (Yuflyma unbranded) SC**
• **Adalimumab-fkjp (Hulio unbranded) SC**
• **Amjevita (adalimumab-atto) SC**
• **Hadlima (adalimumab-bwwd) SC**
• **Hulio (adalimumab-fkjp) SC**
• **Humira (adalimumab) (Cordavis) [NDCs starting with 83457] SC**
	Abrilada (adalimumab-afzb), adalimumab-aacf (Idacio unbranded), adalimumab-aaty (Yuflyma unbranded), adalimumab-fkjp (Hulio unbranded), Amjevita (adalimumab-atto), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Humira (adalimumab) (Cordavis) [NDCs starting with 83457], Hyrimoz (adalimumab-adaz) (Cordavis) [NDCs starting with 83457], Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty), and Yusimry (adalimumab-aqvh) may be considered medically necessary for the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis when:
	• Individual is ≥ 2 years of age
	AND
	• Individual has tried one of the following therapies:
	  ○ Periocular, intraocular, or systemic corticosteroids
	  ○ Immunosuppressives
	AND

Agent	Medical Necessity

• **Hyrimoz (adalimumab-adaz) (Cordavis) [NDCs starting with 83457] SC**
• **Idacio (adalimumab-aacf) SC**
• **Yuflyma (adalimumab-aaty) SC**
• **Yusimry (adalimumab-aqvh) SC**
 	
Managed under pharmacy benefit
	• Individual has had an inadequate response or intolerance to ALL the following agents:
	  ○ Cyltezo (adalimumab-adbm) OR adalimumab-adbm (Cyltezo unbranded)
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314] OR adalimumab-adaz (Hyrimoz unbranded)
	  ○ Simlandi (adalimumab-ryvk) OR adalimumab-ryvk (Simlandi unbranded)
	AND
	• The medication is prescribed by or in consultation with an ophthalmologist

Giant Cell Arteritis	
IL-6 Antagonist • **Actemra (tocilizumab) SC, IV** **Managed under pharmacy and medical benefit**	**Actemra (tocilizumab) may be considered medically necessary for the treatment of giant cell arteritis when:** • Individual is ≥ 18 years of age **AND** • Individual has tried one systemic corticosteroid **AND** • The medication is prescribed by or in consultation with a rheumatologist
Cytokine Release Syndrome	
IL-6 Antagonist • **Actemra (tocilizumab) IV** **Managed under medical benefit**	**Actemra (tocilizumab) may be considered medically necessary for adults and pediatric individuals when the following criteria are met:** • Individual is 2 years of age or older **AND** • Documented chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome
Behcet's Disease	
Phosphodiesterase 4 (PDE4) inhibitor • **Otezla (apremilast) Oral** **Managed under pharmacy benefit**	**Otezla (apremilast) may be considered medically necessary for the treatment of oral ulcers associated with Behcet's Disease when:** • Individual is ≥ 18 years of age **AND**

Agent	Medical Necessity
	• Individual has tried one other systemic therapy (e.g., colchicine, corticosteroids, azathioprine) **AND** • The medication is prescribed by or in consultation with a rheumatologist or dermatologist
Neuromyelitis Optica Spectrum Disorder (NMOSD)	

CD19-directed cytolytic antibody
• **Uplizna (inebilizumab-cdon) IV**
 	
Managed under medical benefit
	Uplizna (inebilizumab-cdon) is subject to review for site of service administration.
	
	Uplizna (inebilizumab-cdon) may be considered medically necessary for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult individuals who are anti-aquaporin-4 (AQP4) antibody positive when the following are met:
	• Individual is 18 years of age or older
	AND
	• Documented diagnosis of NMOSD confirmed by:
	  ○ At least one of the following core clinical characteristics:
	  ▪ Optic neuritis
	  ▪ Acute myelitis
	  ▪ Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
	  ▪ Acute brainstem syndrome
	  ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
	  ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions
	  AND
	  ○ Positive test for AQP4-IgG antibodies
	  AND
	  ○ Exclusion of alternative diagnoses (e.g., multiple sclerosis)
	AND
	• History of at least 1 relapse in last 12 months or 2 relapses in the last 24 months
	AND

Agent	Medical Necessity
	• Expanded Disability Status Scale (**EDSS**) score ≤ 7.5

Interleukin-6 (IL-6) receptor antagonist
• **Enspryng (satralizumab-mwge) SC**
 	
Managed under pharmacy and medical benefit
	Enspryng (satralizumab-mwge) may be considered medically necessary for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult individuals who are anti-aquaporin-4 (AQP4) antibody positive when the following are met:
	• Individual is 18 years of age or older
	AND
	• Documented diagnosis of NMOSD confirmed by:
	  ○ At least one of the following core clinical characteristics:
	  ▪ Optic neuritis
	  ▪ Acute myelitis
	  ▪ Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
	  ▪ Acute brainstem syndrome
	  ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
	  ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions
	  AND
	  ○ Positive test for AQP4-IgG antibodies
	  AND
	  ○ Exclusion of alternative diagnoses (e.g., multiple sclerosis)
	AND
	• History of at least 1 relapse in last 12 months or 2 relapses in the last 24 months
	AND
	• Expanded Disability Status Scale (**EDSS**) score ≤ 6.5

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)	
Interleukin-1 Blocker • **Arcalyst (rilonacept) SC** **Managed under pharmacy and medical benefit**	**Arcalyst (rilonacept) may be considered medically necessary for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) when the following criteria are met:** • Genetic testing has confirmed a mutation in the IL1RN gene **AND** • Individual weight is ≥ 10 kg

Agent	Medical Necessity
	AND • Arcalyst (rilonacept) is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist
Interleukin-1 Receptor Antagonist • **Kineret (anakinra) SC** **Managed under pharmacy and medical benefit**	**Kineret (anakinra) may be considered medically necessary for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) when the following criteria are met:** • Genetic testing has confirmed a mutation in the IL1RN gene **AND** • Kineret (anakinra) is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist
Recurrent Pericarditis	

Interleukin-1 Blocker
• **Arcalyst (rilonacept) SC**
 	
Managed under pharmacy and medical benefit
	Arcalyst (rilonacept) may be considered medically necessary for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence when the following criteria are met:
	• Individual is 12 years of age or older
	AND
	• Documented prior episode of acute pericarditis
	AND
	• Individual has typical pleuritic chest pain plus ≥ 1 of the following:
	  ○ Fever
	  ○ Pericardial rub
	  ○ ECG changes
	  ○ New or worsening pericardial effusion
	  ○ Elevation of markers of inflammation (elevation in white blood cell count, erythrocyte sedimentation rate, or C-reactive protein)
	  OR
	  ○ There is evidence of pericardial inflammation on cardiovascular magnetic resonance (CMR) or computed tomography (CT) after a ≥ 4-week symptom-free interval
	AND
	• Individual has received prior treatment for RP with an NSAID or corticosteroid unless contraindicated
	AND

Agent	Medical Necessity
	• Arcalyst (rilonacept) is prescribed by or in consultation with a cardiologist
Periodic Fever Syndromes & Still's Disease	

Interleukin-1 Blocker
• **Arcalyst (rilonacept) SC**
 	
Managed under pharmacy and medical benefit
	Arcalyst (rilonacept) may be considered medically necessary for the treatment of:
	• Cryopyrin-associated periodic syndromes (CAPS), in adults and children 12 years of age and older, including:
	  ○ Familial cold auto-inflammatory syndrome (FCAS)
	  ○ Muckle-Wells syndrome (MWS)
	AND
	• Arcalyst (rilonacept) is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist

Interleukin-1β blocker
• **Ilaris (canakinumab) SC**
 	
Managed under pharmacy and medical benefit
	Ilaris (canakinumab) may be considered medically necessary for the treatment of:
	• Periodic Fever Syndromes:
	  ○ Cryopyrin-associated periodic syndromes (CAPS), in adults and children 4 years of age and older, including:
	  ▪ Familial cold auto-inflammatory syndrome (FCAS)
	  ▪ Muckle-Wells syndrome (MWS)
	  ○ Tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric individuals 2 years of age and older
	  ○ Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric individuals 2 years of age and older
	  ○ Familial Mediterranean fever (FMF) in adult and pediatric individuals 2 years of age and older
	• Active Still's disease, including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in individuals 2 years of age and older
	AND
	• Ilaris (canakinumab) is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist

Interleukin-1 Receptor Antagonist • **Kineret (anakinra) SC**	**Kineret (anakinra) may be considered medically necessary for the treatment of cryopyrin-associated periodic syndromes (CAPS) when the following criteria are met:**

Agent	Medical Necessity
Managed under pharmacy and medical benefit	• The individual has been diagnosed with neonatal-onset multisystem inflammatory disease (NOMID) **AND** • Kineret (anakinra) is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist
Graft Versus Host Disease	
Orencia (abatacept) **Managed under pharmacy and medical benefit**	**Orencia (abatacept) may be considered medically necessary for the prevention of acute graft versus host disease when the following conditions are met:** • Individual is 2 years of age or older **AND** • The individual will also receive standard therapy with a calcineurin inhibitor (cyclosporine or tacrolimus) **AND** • The individual will also receive standard therapy with methotrexate **AND** • Individual will undergo hematopoietic stem cell transplantation from a matched unrelated donor OR a 1-allele-mismatched unrelated donor **AND** • The medication is being prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center
Rezurock (belumosudil) **Managed under pharmacy benefit**	**Rezurock (belumosudil) may be considered medically necessary for the treatment of chronic graft versus host disease when the following conditions are met:** • The individual is 12 years of age or older **AND** • The individual has tried and failed at least two systemic treatments such as cyclosporine, ibrutinib, mycophenolate mofetil, ruxolitinib, sirolimus, or tacrolimus **AND** • The medication is being prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center **AND**

Agent	Medical Necessity
	• The dose is limited to 200 mg daily
Myasthenia Gravis	
Rystiggo (rozanolixizumab-noli) **Managed under medical benefit**	**Rystiggo (rozanolixizumab-noli) may be considered medically necessary for the treatment of myasthenia gravis when the following criteria are met:** • Individual is 18 years of age or older **AND** • A diagnosis of myasthenia gravis with a serological test for anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibodies **AND** • Currently using the acetylcholinesterase inhibitor pyridostigmine, has tried and failed pyridostigmine or has contraindications to use of pyridostigmine **AND** • Individual is currently using two or more immunosuppressive therapies (ISTs) (e.g., glucocorticoids, azathioprine, mycophenolate mofetil, cyclosporine) or has tried and failed two ISTs or has contraindications that prevent use of two ISTs **AND** • Medication is not being used concurrently with Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Zilbrysq (zilucoplan)
Vyvgart (efgartigimod alfa-fcab) **Managed under medical benefit**	**Vyvgart (efgartigimod alfa-fcab) may be considered medically necessary for the treatment of myasthenia gravis when the following criteria are met:** • Individual is 18 years of age or older **AND** • A diagnosis of myasthenia gravis with a serological test for anti-acetylcholine receptor (AChR) antibodies **AND** • Individual is currently using two or more immunosuppressive therapies (ISTs) (e.g., glucocorticoids, azathioprine, mycophenolate mofetil, cyclosporine) or has tried and failed two ISTs or has contraindications that prevent use of two ISTs **AND**

Agent	Medical Necessity
	• Medication is not being used concurrently with Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Rystiggo (rozanolixizumab-noli), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Zilbrysq (zilucoplan)
Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **Managed under medical benefit**	**Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) may be considered medically necessary for the treatment of myasthenia gravis when the following criteria are met:** • Individual is 18 years of age or older **AND** • A diagnosis of myasthenia gravis with a serological test for anti-acetylcholine receptor (AChR) antibodies **AND** • Individual is currently using two or more immunosuppressive therapies (ISTs) (e.g., glucocorticoids, azathioprine, mycophenolate mofetil, cyclosporine) or has tried and failed two ISTs or has contraindications that prevent use of two ISTs **AND** • Medication is not being used concurrently with Vyvgart (efgartigimod alfa-fcab), Rystiggo (rozanolixizumab-noli), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Zilbrysq (zilucoplan)
Primary Immunoglobulin A Nephropathy (IgAN)	
Filspari (sparsentan) **Managed under pharmacy benefit**	**Filspari (sparsentan) may be considered medically necessary to reduce proteinuria with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression when the following criteria are met:** • Individual is 18 years of age or older **AND** • Documented diagnosis of biopsy-proven primary immunoglobulin A nephropathy (IgAN) **AND** • Documented urine protein-to-creatinine ratio (UPCR) $\geq$1.5g/g **AND** • Tried and failed an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) **AND**

Agent	Medical Necessity
	• Filspari (sparsentan) is not used concurrently with other ACE inhibitors, ARB, endothelin receptor antagonists (ERAs), and aliskiren **AND** • Filspari (sparsentan) is prescribed by or in consultation with a nephrologist **AND** • The dose prescribed is limited to 400 mg per day
Tarpeyo (budesonide)	**Tarpeyo (budesonide) may be considered medically necessary to reduce the loss of kidney function with primary immunoglobulin A nephropathy (IgAN) at risk of disease progression when the following criteria are met:** • Individual is 18 years of age or older **AND** • Documented diagnosis of biopsy-proven primary immunoglobulin A nephropathy (IgAN) **AND** • Documented urine protein-to-creatinine ratio (UPCR) $\geq$1.5g/g **AND** • Used in combination with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) **AND** • Tarpeyo (budesonide) is prescribed by or in consultation with a nephrologist **AND** • The dose prescribed is limited to 16 mg daily **AND** • The total duration of therapy is limited to 9 months

Agent	Investigational
As listed	**All other uses of the above-named agents when used in combination with each other, in quantities that exceed the FDA labeled dosing for condition, or for conditions not outlined in this policy or policies 5.01.550 and 5.01.563 are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Future re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J0129	Injection, abatacept (Orencia), 10 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J0135	Injection, adalimumab (Humira), 20mg
J0490	Injection, belimumab (Benlysta), 10 mg
J0491	Injection, anifrolumab-fnia (Saphnelo), 1 mg
J0638	Injection, canakinumab, (Ilaris)1 mg
J1438	Injection, etanercept (Enbrel), 25mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J1745	Injection, infliximab, excludes biosimilar (Remicade or Janssen unbranded), 10mg
J1823	Injection, inebilizumab-cdon, (Uplizna) 1 mg
J2793	Injection, rilonacept, (Arcalyst) 1 mg
J3262	Injection, tocilizumab, (Actemra) 1 mg

Code	Description
J3590	Unclassified biologics (Use to report Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Enspryng (satralizumab-mwge), Hadlima (adalimumab-bwwd), Hyrimoz (adalimumab-adaz), Hulio (adalimumab-fkjp), Kineret (anakinra), Rystiggo (rozanolixizumab-noli), Simlandi (adalimumab-ryvk), Yuflyma (adalimumab-aaty), Yusimry (adalimumab-aqvh)
J9332	Injection, efgartigimod alfa-fcab,(Vyvgart) 2 mg
J9333	Injection, rozanolixizumab-noli (Rystiggo), 1 mg (new code effective 1/1/2024)
J9334	Injection, efgartigimod alfa, 2 mg and hyaluronidase-qvfc (new code effective 1/1/2024)
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Age limits specified in this policy are determined according to US Food and Drug Administration (FDA)-approved indications, where applicable.

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Benefit Application

Pharmacy Benefit

Cosentyx (secukinumab), Filspari (sparsentan), Lupkynis (voclosporin), Otezla (apremilast), Rezurock (belumosudil), and Tarpeyo (budesonide) are managed through the pharmacy benefit.

Medical Benefit

Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), Remicade (infliximab), Renflexis (infliximab-abda), Saphnelo (anifrolumab-fnia), Uplizna (inebilizumab-cdon), Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), and Rystiggo (rozanolixizumab-noli) are managed through the medical benefit.

Medical / Pharmacy Benefit

Abrilada (adalimumab-afzb), Actemra (tocilizumab), adalimumab-aacf (Idacio unbranded), adalimumab-aaty (Yuflyma unbranded), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi), Amjevita (adalimumab-atto), Benlysta (belimumab), Cyltezo (adalimumab-adbm), Enbrel (etanercept), Enspryng (satralizumab-mwge), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Humira (adalimumab), Hyrimoz (adalimumab-adaz), Ilaris (canakinumab), Kineret (anakinra), Orencia (abatacept), Simlandi (adalimumab-ryvk), Yuflyma (adalimumab-aaty), and Yusimry (adalimumab-aqvh) are managed through both the pharmacy and medical benefit.

Evidence Review

Miscellaneous Autoimmune Diseases

TNF inhibitors, rituximab and various other agents have been used off-label to treat a variety of autoimmune diseases. Most of this use represents significant unmet medical needs for chronic diseases with few treatment options.

Hidradenitis Suppurativa

Hidradenitis Suppurativa (HS) is an inflammatory skin disease affecting an estimated 1 to 4% of the world population. The main features of HS include painful and chronically recurring, deep-seated follicular nodules, papules, pustules, and abscesses, scarring, sinus tracts, and recurrent discharge. The area's most commonly affected are the under the arms, groin, buttocks, and under the breasts. The disease is variable and recurrent. It may occur as solitary or multiple lesions in one area, or in many areas. In more severe cases, there may be large areas of skin affected by recurrent, draining lesions.

The FDA approved Humira (adalimumab) to treat individuals with HS.

Two randomized, double-blind, placebo-controlled studies (Studies HS-I and II) evaluated the safety and efficacy of Humira in a total of 633 adult subjects with moderate to severe hidradenitis suppurativa (HS) with Hurley Stage II or III disease and with at least 3 abscesses or inflammatory nodules. In both studies, subjects received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 and continued through Week 11. Subjects used topical antiseptic wash daily. Concomitant oral antibiotic use was allowed in Study HS-II.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to baseline (see Table below). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in individuals who entered the study with an initial baseline score of 3 or greater on a 11-point scale.

In both studies, a higher proportion of Humira than placebo-treated subjects achieved HiSCR (see **Table 1** below).

Table 1. Efficacy Results at 12 Weeks in Subjects with Moderate to Severe Hidradenitis Suppurativa

	HS Study I		HS Study II*	
	Placebo	Humira 40 mg Weekly	Placebo	Humira 40 mg Weekly

	HS Study I		HS Study II*	
Hidradenitis Suppurativa Clinical Response (HiSCR)	N=154, 40 (26%)	N=153, 64 (42%)	N=163, 45 (28%)	N=163, 96 (59%)

*19.3% of subjects in Study HS-II continued baseline oral antibiotic during the study.

In both studies, from Week 12 to Week 35 (Period B), subjects who had received Humira were re-randomized to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo). Subjects who had been randomized to placebo were assigned to receive Humira 40 mg every week (Study HS-I) or placebo (Study HS-II).

During Period B, flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from Humira treatment following the primary efficacy time point in two studies.

Cosentyx (secukinumab)

Two randomized, double-blind, placebo-controlled 52-week Phase 3 trials (i.e., HS Trial 1 [NCT03713619] and HS Trial 2 [NCT03713632]) assessed the efficacy and safety of Cosentyx in the treatment of adult individuals with moderate to severe hidradenitis suppurativa (HS). In both trials, subjects were randomized to placebo or Cosentyx 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks or every 4 weeks. At Week 16, subjects who were randomized to placebo were reassigned to receive Cosentyx 300 mg at Weeks 16, 17, 18, 19, and 20 followed by either Cosentyx 300 mg every 2 weeks (Q2W) or Cosentyx 300 mg every 4 weeks (Q4W). In HS Trial 1 and HS Trial 2, a statistically significantly higher proportion of subjects treated with Cosentyx 300 mg every 2 weeks (after the first four weeks) achieved a HiSCR50 response at Week 16 compared to individuals treated with placebo. In both HS trials, a higher proportion of subjects treated with Cosentyx 300 mg every 4 weeks (after the first four weeks) achieved HiSCR50 at Week 16 compared to subjects treated with placebo, where statistical significance was reached in HS Trial 2. In both trials, the onset of action of Cosentyx occurred as early as Week 2 and the efficacy progressively increased up to Week 16.

Lupus – Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a chronic, complicated, progressive autoimmune disease impacting multiple organ systems. It is a condition characterized by auto-reactive B-cells. Autoantibody production from such abnormal B lymphocyte function leads to chronic inflammation and cellular, tissue and organ damage. Diverse in presentation, individuals with SLE experience mild to life-threatening manifestations and unpredictable clinical course of exacerbations and remissions. As symptoms are non-specific, the identification of SLE is often-times delayed. It has been reported that individuals visit a mean of three different physicians and an average of 4 years after the onset of symptoms before a correct diagnosis is reached.

The mucocutaneous (rash), articular (arthritis), serosal (pleuritis, pericarditis), renal (proteinuria) and neurologic (seizures, psychosis) clinical features, as well as hematologic and immunologic laboratory findings, incorporated in the American College of Rheumatology SLE diagnosis classification criteria reflects the heterogeneity of the disease. Most commonly involved organs include the skin, musculoskeletal, renal, nervous, cardiovascular and pulmonary systems. Over 75% of SLE individuals have debilitating, generally non-fatal mucocutaneous (rash) and musculoskeletal involvement (arthritis). A smaller SLE population (50%-66%) is afflicted with renal disorders and is associated with poorer outcome and mortality. About 2/3 of SLE individuals also present with varying severity of neuropsychiatric manifestations ranging from mood disorders, anxiety, psychosis to seizures. Other less common but serious manifestations include serositis (16 to 64%), neurological disorders (9 to 36%), and immune-mediated cytopenia's (4 to 43%). Depression is common among people with chronic autoimmune disease. Overall, SLE individuals have a 2-5 times greater mortality rate.

As endogenous female sex hormone is identified to have a role in SLE development, SLE is found primarily in women (90% of SLE population are female, 6-10 female:1 male), typically 15-44 years of age. In the US, more than 300,000 people have SLE and an annual incident rate of 15,000. 4 million people are impacted worldwide.

While SLE individuals have at least twice the mortality risk relative to the general population, survival rate at 15 years improved dramatically from 50% in the 1950s to currently greater than 80%. Most common causes of death are cardiovascular disease, infections, renal disease and complications due to SLE disease activity.

In addition to gender, ethnicity has an influence on the development of SLE. Mestizo, indigenous Americans, Blacks and Asians have more severe SLE disease and poorer clinical progression. Blacks are three times more likely than Caucasians to have SLE. Asian and African American SLE individuals develop renal disease more frequently than those of European descent (60-70%, 50%, 20-30%, respectively).

SLE is characterized by auto-reactive B-cells. Autoantibody production from such abnormal B lymphocyte function leads to chronic inflammation. Autoantibody complex, cytokines and complement activation represent mediators of tissue damage in SLE individuals. Anti-nuclear antibody (ANA) is found present in more than 90% of individuals. Those positive are more likely to have active lupus associated with B-cell dysfunction. Anti-dsDNA, a type of ANA, is one of the diagnosis criteria established by the American College of Rheumatology and is monitored as gauge of SLE disease response to treatment. Consistent with existing pathophysiology, inhibition of BlyS, an endogenous protein responsible for B-cell homeostasis, decreases autoreactive B-cell activity and serological changes. Transgenic animals overexpressing BlyS have lupus-like syndrome, increased immunoglobulins and immune complex depositions. BlyS is also found elevated in human autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and Sjogren's.

Most individuals present with generalized symptoms of fatigue, fever, anorexia, weight loss, photosensitivity, malar rash, oral ulcers, arthralgia, and hair loss. Incompletely controlled SLE can progress to end-stage organ involvement; SLE activity of 60% of SLE individuals is found to worsen within 2-7 years of diagnosis. Irreversible cellular and tissue damages can accumulate to result in life-threatening renal, cardiac, pulmonary, CNS and hematological system toxicities. The subsequent development of pleuritis, pericarditis, stroke, seizure, nephritis, vasculitis, anemia, thrombocytopenia and other blood dyscrasias present significant mortality and morbidity risks.

Aside from these autoimmune mediated disease manifestations, SLE individual are in high risk for infections of the respiratory and urinary systems, cardiovascular diseases, hematological and solid tumors, maternal and fetal morbidity and mortality (spontaneous abortions, pre-eclampsia, intrauterine growth impairment, premature birth). Most common causes of death are infections, renal disease, cardiovascular disease and complications due to SLE disease activity.

The current SLE standard of care is similar across the world. Treatment of mild-to-moderate symptoms involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial drugs such as hydroxychloroquine and corticosteroids such as prednisone and its equivalent. For life-threatening manifestations such as the renal, CNS, cardiovascular and pulmonary systems, aggressive single or combination of treatments with high dose corticosteroids and immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate and mycophenolate is used. Corticosteroids, hydroxychloroquine and aspirin have FDA approved SLE indications.

Particularly for individuals with active and life-threatening disease activity, SLE remains an unmet medical disease. The very treatments used to alleviate lupus symptoms have poor tolerability and short- and long-term morbidity risks. Ones used for mild/mod SLE flares involves nonspecific immune system suppression. Aggressive treatments such as cyclophosphamide is

associated with gonadal toxicity, whereas high dose corticosteroids (>7.5 mg/day, cumulative doses >365g) can lead to cataracts, osteoporosis, metabolic disorders, increased infections, edema, weight gain and hyperlipidemia. This is especially concerning as SLE individuals tend to be young women of childbearing age, have lower immune system and greater cardiovascular risks due to the nature of the underlying autoimmune disease. Currently there is no approved SLE treatment shown to prolong survival or reverse the course of the disease.

Benlysta (belimumab)

Benlysta (belimumab) is an FDA-approved 147kDa, recombinant fully human IgG1λ monoclonal antibody. It targets a novel pathway to potentially treat SLE by binding to soluble, endogenous human B-lymphocyte stimulator BlyS (also known as B-cell activating factor or BAFF, TALL-1, THANK, TNFSF13B, zTNF4). The binding inhibits BlyS biological activity of B-cell selection, survival, differentiation and eventual antibody formation of native, activated plasmacytoid and plasma cells.

The efficacy of belimumab was studied in two Phase III trials. SLE Responder Index (SRI) response at 52 weeks, the primary endpoint, was met for belimumab 10 mg/kg treatment arm in both BLISS 52 [1.83 OR (1.30-2.59), p=0.0006] and BLISS76 [1.52 OR (1.07-2.15), p=0.0207]. Overall, secondary endpoints of reduction in severe flare, steroid use, autoantibodies, B-cell subsets, normalization of complement levels and improvement in quality of life were also achieved. 66% of the FDA Arthritis Advisory Committee (10 out of 15) felt the clinical data provided support of efficacy. Concerns were cited over the lack of study consistency within and between the phase 3 studies, lack of statistical significance for some populations and the exclusion of SLE individuals with severe renal or central nervous system diseases. The representative nature of the SLE individuals sampled was also questioned.

The two-Phase III studies were set-up nearly identically, though differences in baseline demographics, serological activity, geographical location and concurrent SLE medication use necessitate their separate analyses. Bliss 76 was conducted in North America and Europe, with 70% Caucasian and 14% African American. Relative to BLISS 52, BLISS 76 had a lower baseline SLE activity (less of SS score >=10, proteinuria>= 2g/24 hours, 1A or 2B BILAG, auto-antibodies, much less prescribed corticosteroid, while using greater NSAIDS and immunosuppressive agents). The data from BLISS 76 clinical trial was less convincing, with its narrower incremental benefit of belimumab over placebo in SRI response, steroid use and SLE flare reduction, lack of efficacy for African American groups, and later onset of significant SS score improvement (32 weeks versus 16 weeks in BLISS 52). With the exception of African American groups, the evidence from BLISS 52 clinical trial was stronger, more robust and consistent across different

ethnicities. A lower number of BLISS 52 participants receiving 10mg/kg belimumab required an increase of corticosteroids. Reduction in flares and prolongation to first flare were seen only in this ex-US-conducted study.

For both studies, disease manifestation resolution often seen in organ systems were those commonly involved at baseline: mucocutaneous (rash, oral ulcers, alopecia), immunologic (serological measures of disease activity, anti-dsDNA and complements) and musculoskeletal (arthritis). SLE activity reduction was also observed with the vascular (vasculitis) and central nervous system (lupus headache), both systems of which were less commonly involved at study initiation. However, resolution of similarly less frequently involved hematology abnormalities and fever was not observed in the belimumab group. The statistically significant difference in improvement from baseline as benchmarked by SRI response was driven largely by improvement of the mucocutaneous and musculoskeletal systems, and not organ systems more associated with poor SLE outcome and mortality (kidneys, central nervous system, blood vessels). Observations of these serious organ manifestations were too uncommon to assess treatment effects.

Subgroup analyses revealed a lack demonstrated efficacy in African American subjects in both Phase III studies, which contradicted the positive treatment response previously observed in LBS02 Phase II trial. Similarly, Native Americans were found more associated with favorable disease activity reduction in BLISS 52 but not its counterpart trial. There was some geographical dependence, as participants from US and Canada had smaller treatment effect compared to some other regions. Since belimumab is to be administered chronically, durability and onset of response are of concern. Of note, differences in efficacy endpoint at the conclusion of BLISS 76 were no longer statistically significant between treatment arms [PLO 32%, 10mg/kg 39%, 1.3 (0.9, 1.9), p=0.13], which was a drop from PLO 34%, 10mg/kg 43% 1.5 (1.07, 2.15), p=0.0207 in the preceding 24 weeks. Dose-response was not consistent; throughout the studies, 1mg/kg was noticed at times to be more, or just as effective as the more potent proposed formulation. Individuals with severe renal or central nervous system (CNS) diseases were not evaluated and therefore efficacy is not known. A disclaimer to this effect was included in the final approved product label.

As safety data were pooled from the three intravenous belimumab clinical studies (LBS02, BLISS 52 and BLISS76) in an attempt to generate a sufficiently large sample of rare events, the ability to detect safety trend concerning specific ethnicity and geological populations was lost. Overall, headache, upper respiratory tract infection and arthralgia were some of the common adverse events experienced by belimumab participants. Pyrexia was the most reported serious adverse event. The investigational drug was found to be associated with greater risk of infection, mortality and psychiatric events ranging from depression, suicidal ideation to suicide. Notably,

no such neuropsychiatric adverse events were seen in those receiving only SLE standard therapy. Malignancy and hypersensitivity rates were comparable to the placebo group. While belimumab has safety signals, its safety profile is favorable and relatively minor compared to the side effects experienced by those on current SLE standard-of-care. 14 of the 15 Advisory Committee members agreed that the clinical data provided adequate safety evidence.

In Trial 4 the safety and efficacy of Benlysta IV was evaluated in an international, randomized, double-blind, placebo-controlled, 52-week, pharmacokinetics (PK), efficacy and safety study conducted in 93 pediatric individuals with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. Individuals had active SLE disease, defined as a SELENA-SLEDAI score ≥6 and positive autoantibodies at screening as defined in the adult trials. Individuals were on a stable SLE treatment regimen (standard of care) and had similar inclusion and exclusion criteria as in the adult studies. The median age was 15 years (range: 6 to 17). The majority (95%) of individuals were female. More than 50% of individuals had 3 or more active organ systems involved at baseline. The most common active organ systems at baseline based on SELENA-SLEDAI were mucocutaneous (91%), immunologic (74%), and musculoskeletal (73%). Overall, 19% of pediatric individuals had some degree of renal activity and less than 7% had activity in the cardio-respiratory, hematologic, CNS or vascular systems. Randomization into age-related treatment cohorts was stratified by screening SELENA-SLEDAI scores (6 to 12 vs >13) and age (5 to 11 years vs 12 to 17 years).

The primary efficacy endpoint was the SLE Responder Index (SRI-4) at Week 52. There was a numerically higher proportion of pediatric individuals achieving a response in SRI-4 and its components in pediatric individuals receiving Benlysta IV plus standard therapy compared with placebo plus standard therapy.

At baseline, 95% of pediatric individuals were receiving prednisone. Among those pediatric individuals, 20% of pediatric individuals receiving Benlysta IV plus standard therapy reduced their average prednisone dose by at least 25% per day during Weeks 44 through 52 compared with 21% of pediatric individuals on placebo plus standard therapy.

In Trial 4, the probability of experiencing a severe SLE flare, as measured by the modified SELENA-SLEDAI Flare Index, excluding severe flares triggered only by an increase of the SELENA-SLEDAI score to >12, was calculated. The proportion of pediatric individuals reporting at least one severe flare during the study was numerically lower in pediatric individuals receiving Benlysta IV plus standard therapy (23%) compared with those receiving placebo plus standard therapy (43%). Pediatric individuals receiving Benlysta IV 10 mg/kg plus standard therapy had a 62% lower risk of experiencing a severe flare during the 52 weeks of observation, relative to the placebo plus standard therapy group. Of the pediatric individuals experiencing a severe flare, the median time to the first severe flare was 160 days in pediatric individuals receiving Benlysta

IV plus standard therapy compared with 82 days in pediatric individuals receiving placebo plus standard therapy.

Saphnelo (anifrolumab-fnia)

Saphnelo (anifrolumab-fnia) is a human IgG1κ monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR) with high specificity and affinity. This binding inhibits type I IFN signaling, thereby blocking the biologic activity of type I IFNs. Anifrolumab also induces the internalization of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signaling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalizes peripheral T-cell subsets. Type I IFNs play a role in the pathogenesis of SLE. Approximately 60-80% of adult individuals with active SLE express elevated levels of type I IFN inducible genes.

Anifrolumab has been studied in two Phase 3 trials for SLE and a Phase IIIb trial extension of a Phase II trial. Anifrolumab is also under study for lupus nephritis (Phase II) and in a subcutaneous format (Phase II).

The TULIP-1 and TULIP-2 trials were 52-week, multicenter, double-blind, randomized, placebo-controlled, Phase III studies. Both trials included individuals 18-70 years of age who met ACR criteria for SLE and who had moderate to severe active disease. This was defined as a Systemic Lupus Erythematosus Dis-ease Activity Index-2000 (SLEDAI-2K) score ≥6 excluding points related to fever, lupus-related headache (HA), or organic brain syndrome and a clinical SLEDAI-2K score without laboratory results of ≥4. Additionally, severe disease activity in ≥1 organ or moderate in ≥2 organs as defined by the BILAG-2004 index (organ domain scores ≥1 A item or ≥2 B items) and physician's global assessment (PGA) ≥1 on a four-point scale visual analogue scale (VAS) scale were required. Individuals were also stable on ≥1 SLE treatment. Individuals with severe lupus nephritis or neuropsychiatric lupus were excluded.

The TULIP-1 trial randomized 457 individuals to anifrolumab 300 mg IV every 4 weeks, anifrolumab 150 mg IV every 4 weeks, or placebo.1 All comparisons were conducted between anifrolumab 300 mg and placebo only. The primary efficacy measure was SRI-4 at 52 weeks while the key secondary endpoints were reduction in steroid dose ≤7.5 mg from week 40-52 if the baseline dose of steroid was ≥10 mg, ≥50% re-duction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score at week 12 in individuals with moderate to severe cutaneous activity (CLASI ≥10 at baseline), annualized flare rate at Week 52, SRI-4 at Week 24, and SRI-4 at Week 52 in individuals with high IFN gene signature (IFNGS) status. BICLA response

at Week 52 was assessed as an "other" secondary endpoint. The primary outcome of SRI-4 response was defined as ≥4 point reduction in SLEDAI-2K from baseline, no new disease activity in any organ (defined as ≥1 new BILAG A item or ≥2 BILAG B items), no worsening in PGA score (defined as ≥0.3 points increase from baseline), and no study treatment discontinuation or use of restricted medications beyond protocol-allowed thresholds. Anifrolumab did not meet the primary outcome of SRI-4 at 52 weeks (36% anifrolumab vs 40% placebo, p=0.412); therefore, all secondary endpoints were considered nominal. Key secondary outcomes of reduction steroid dose, annualized flare rate, SRI-4 response at 24 weeks, and SRI-4 response in individuals with high IFNGS did not reach significance. However, more individuals in the anifrolumab group achieved ≥50% reduction in CLASI score from baseline at week 12 than placebo (42% vs 25%, nominal p=0.005). Of note, the original study protocol considered individuals with new NSAIDs or an NSAID dose change as nonresponders. The authors stated these original rules were in-consistent with the intention of the protocol and were inappropriate. The sponsor and a group of SLE experts revised the study rules and instituted a post-hoc amendment which considered individuals non-responders only if changes in NSAID use occurred during the last 2 weeks of the study. However, no significant difference in the primary outcome of SRI-4 at 52 weeks was identified between groups despite the amendment (47% anifrolumab vs 43% placebo, p=0.455).

The TULIP-2 trial randomized 365 individuals to anifrolumab 300 mg IV every 4 weeks or placebo. The primary efficacy measure was changed during the study from SRI-4 to the difference in BICLA response between groups at week 52. This occurred before unblinding of the data and was done in response to the results of the TULIP-1 trial. BICLA response was defined as all of the following: 1) reduction of all severe or moderately severe (BILAG A or B) disease activity at baseline to lower levels and no worsening in other organ systems (worsening defined as ≥1 new BILAG A item or ≥2 BILAG B items); 2) no worsening in disease activity per SLEDAI-2K score and PGA score (defined as no increase of ≥0.3 from baseline); 3) no discontinuation of trial intervention; and 4) no use of restricted medications beyond protocol-allowed thresholds. Key secondary endpoints included BICLA response at Week 52 in individuals with high IFNGS at baseline, reduction in steroid dose to ≤7.5 mg/day from week 40-52 if baseline dose was ≥10 mg/d; ≥50% reduction in CLASI at week 12 in individuals with moderate to severe cutaneous activity defined as CLASI ≥10, ≥50% reduction in swollen or tender joints at week 52 in individuals with ≥6 swollen and ≥6 tender joints at baseline, and annualized flare rate at Week 52. NSAID rules consistent with the post-hoc amendment from the TULIP-1 trial were used in the TULIP-2 trial. Anifrolumab significantly increased the primary outcome of the BICLA response at 52 weeks compared to placebo (47.8% vs 31.5%, p=0.001). Additionally, anifrolumab significantly improved the key secondary outcomes of BICLA at 52 weeks in individuals with high IFNGS, reduced steroid dose, reduction in CLASI activity, and annualized fare rate compared to placebo. There was no difference between groups in reduction in swollen and tender joints

(p=0.55). SRI-4 results were not considered key and were not multiplicity adjusted. The difference be-tween groups in SRI-4 at 52 weeks was 18.2% (95% confidence interval [CI] 8.1-28.3), favoring anifrolumab.

Pyoderma Gangrenosum

Pyoderma gangrenosum is an inflammatory disease with dermatologic manifestations including painful ulcerations with erythematous borders. It is presumed to be autoimmune in origin, though the mechanism is not well understood. Lesions usually develop at sites of minor skin injury, usually on the lower extremities. These lesions can grow in size and become necrotic. Underlying fasciitis may occasionally develop from them. Some individuals develop pustular, bullous or vegetative lesions. Other common sites are colostomies and paraneoplastic lesions in individuals with hematologic malignancies. Progress of the lesions is highly variable, and individual response to treatment is heterogeneous. Obesity, diabetes or edema may be contributing factors.

Due to the infrequent occurrence and heterogeneity of pyoderma gangrenosum, the treatment approach is empiric and individual specific. First-line options include topical tacrolimus, nicotine, and 5-ASA, systemic corticosteroids and immunosuppressant agents such as azathioprine, cyclosporine, methotrexate and mycophenolate. When these approaches fail, biologic therapy is usually tried. Successful treatment with TNF inhibitors (etanercept, adalimumab, infliximab) has been reported. Response to ustekinumab and various investigational interleukin inhibitors has also been reported. Surgical management is another option.

Wegener's Granulomatosis and Microscopic Polyangiitis

Wegener's granulomatosis (WG) is an autoimmune vasculitis that may affect various internal organs and can be potentially life-threatening. Symptoms vary and can mimic a variety of other diseases, making it difficult to diagnose. These include rhinitis, glomerulonephritis, pulmonary nodules and hemorrhage, neuropathies, gastrointestinal symptoms and various other inflammatory manifestations. The disease can occur at any age, usually in adults.

WG can be recognized by the distinctive triad of granulomatous inflammation, necrosis, and vasculitis of the respiratory tract. Vasculitis in other regions is also common. It can follow a varied clinical course that is strongly influenced by treatment. Untreated, generalized WG is usually lethal. Historically, treatment with immunosuppressants has been used. Glucocorticoids and cyclophosphamide have been a standard therapy, but this is limited by cyclophosphamide

toxicity. If remission is achieved, less toxic agents such as azathioprine may be employed for maintenance.

The FDA has approved rituximab in combination with glucocorticoids, to treat individuals with WG and microscopic polyangiitis (MPA). Both of these diseases affect people of all ages and ethnicities, and both genders. The causes of these disorders are unknown, and both are considered orphan diseases because they each affect less than 200,000 people in the United States.

Giant Cell Arteritis

Giant cell arteritis (GCA) is an inflammation of the lining of the arteries. It affects the arteries in the head, especially those in the temples. Temporal arteritis is another name for this disease. GCA frequently causes headaches, scalp tenderness, jaw pain, and vision problems.

The safety of subcutaneous Actemra (tocilizumab) has been studied in one Phase III study (WA28119) with 251 GCA individuals. The total individual years duration in the Actemra GCA all exposure population was 138.5 individual years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the Actemra treatment groups was generally consistent with the known safety profile of Actemra. There was an overall higher incidence of infections in GCA individuals relative to RA individuals. The rate of infection/serious infection events was 200.2/9.7 events per 100 individual years in the Actemra weekly group and 160.2/4.4 events per 100 individual years in the Actemra every other week group as compared to 156.0/4.2 events per 100 individual years in the placebo + 26-week prednisone taper and 210.2/12.5 events per 100 individual years in the placebo + 52-week taper groups.

Neuromyelitis Optica Spectrum Disorders

Neuromyelitis optica spectrum disorders (NMOSD), previously known as Devic disease or neuromyelitis optica (NMO) are CNS inflammatory disorders characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Differential diagnosis is from RRMS. Presentation is generally bilateral and monophasic and may be difficult to distinguish from MS due to variability in presentation and clinical course, but once diagnosed, a different treatment strategy is indicated. Hallmark features include acute attacks of bilateral or rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically

relapsing course. Attacks most often occur over days, with variable degrees of recovery over weeks to months. Other suggestive symptoms include episodes of intractable nausea, vomiting, hiccups, excessive daytime somnolence or narcolepsy, reversible posterior leukoencephalopathy syndrome, neuroendocrine disorders, and (in children) seizures. While no clinical features are disease-specific, some are highly characteristic. Optic neuritis presents with varying degrees of vision loss and is almost always associated with eye pain that worsens with movement of the eye.

Reported prevalence of NMOSD ranges from 0.5 to 10 per 100,000. The reported incidence of NMOSD in women is 5-10 times higher than in men. Median age of onset is 32 to 40, it sometimes occurs in children or older adults. It may be overrepresented in some non-European populations, including Africans, East Asians, and Latin Americans, MS is less prevalent. Reported prevalence is higher among black compared with white individuals, but the evidence for this is relatively weak. In Japan, optic-spinal multiple sclerosis (OSMS), represents approximately 15 to 40 percent of MS. Whether NMOSD and Asian OSMS are the same remains uncertain. NMOSD is usually sporadic, though a few familial cases have been reported.

NMOSD has a relapsing course in most cases. In some individuals, optic neuritis and transverse myelitis occur concurrently; in others, clinical episodes are separated by a variable time delay. Relapse occurs within the first year following an initial event in 60 percent of individuals and within three years in 90 percent. As a rule, severe residual deficits follow initial and subsequent attacks, leading to rapid development of disability due to blindness and paraplegia within five years.

MS is mostly cell-mediated, while NMOSD is thought to be primarily mediated by the humoral immune system. Damage is to both gray and white matter of the optic nerves and associated spinal segments. A disease-specific serum NMO-immunoglobulin G (IgG) antibody selectively binds aquaporin-4 (AQP4), previously known as NMO IgG. Presence of aquaporin-4 (AQP4)-immunoglobulin G (IgG) antibodies is required for definitive diagnosis. Serum anti-AQP4 titers correlate with clinical disease activity, drop after immunotherapy, and remain low during remissions. Titers at the nadir of attacks correlate with spinal cord damage. AQP4 is a water channel protein. AQP4-IgG antibodies that bind to astrocyte AQP4 water channels, leading to astrocyte dysfunction and the clinical manifestations of nausea and vomiting. A potential subset of individuals have anti-myelin oligodendrocyte glycoprotein (MOG).

NMOSD is frequently associated with systemic autoimmune disorders, including hypothyroidism, pernicious anemia, ulcerative colitis, myasthenia gravis, and idiopathic thrombocytopenic purpura; systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren syndrome, and sometimes with neoplasms.

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disease mainly characterized by fatigue and muscle weakness in ocular, limb, and respiratory muscles. Many individuals also experience bulbar weakness, which refers to an impairment of the lower cranial nerves. This results in difficulty talking, chewing, swallowing, and holding up the head. The degree of muscle weakness can fluctuate and vary in severity from person to person; however, it will generally improve with rest and worsen with physical activity. Other precipitating factors include pregnancy, infection, surgery, and stress. The cause of MG is unknown, but it is usually diagnosed in young women (20 to 30 years of age) or men ≥50 years of age. The life expectancy for MG individuals is near normal. The mortality rate is now about 3%, mainly due to the risk of myasthenic crisis, a potentially life-threatening complication in which muscle weakness causes respiratory failure. The muscle weakness presenting in MG is due to an antibody-mediated immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction. Myasthenia gravis has been associated with antibodies against 3 postsynaptic proteins: acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (LRP4). AChR antibody–positive individuals represent the vast majority of gMG individuals.

Vyvgart (efgartigimod alfa-fcab)

Vyvgart is a first-in-class human immunoglobulin G1 (IgG1) antibody fragment that binds the neonatal Fc receptor (FcRn), keeping antibodies in circulation and preventing FcRn from recycling IgG back into the blood. This causes a reduction in overall levels of IgG, including the abnormal AChR antibodies that are present in most individuals with gMG. Vyvgart was evaluated in the Phase 3 ADAPT trial, a 26-week randomized, double-blind, placebo-controlled study that was conducted in North America, Europe, and Japan. Study participants were ≥18 years of age with class II to IV gMG. These individuals were eligible to participate in the study regardless of AChR antibody status if they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 (>50% non-ocular) and were on a stable dose of at least 1 treatment for gMG. The primary analysis of ADAPT was completed in a modified intention-to-treat population of all AChR antibody–positive individuals who had a valid baseline MG-ADL assessment and at least 1 post-baseline MG-ADL assessment. Participants were randomly assigned (1:1) to Vyvgart (10 mg/kg) or matching placebo, administered as 4 infusions per cycle (1 infusion per week), repeated as needed depending on clinical response no sooner than 8 weeks after initiation of the previous cycle. The efficacy of Vyvgart was measured using the Myasthenia Gravis-Specific

Activities of Daily Living scale (MG-ADL) which assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. A total score ranges from 0 to 24, with the higher scores indicating more impairment. In this study, an MGADL responder was defined as an individual with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle. The primary efficacy endpoint was the comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the AChR-Ab positive population. A statistically significant difference favoring Vyvgart was observed in the MG-ADL responder rate during the first treatment cycle [67.7% in the Vyvgart-treated group vs 29.7% in the placebo-treated group ($p<0.0001$)].

The safety analysis included all randomly assigned individuals who received at least 1 dose or partial dose of Vyvgart or placebo. In the ADAPT trial, 77% of individuals in the Vyvgart group and 84% of individuals in the placebo group had treatment-emergent adverse events; the most frequent of which were headache (Vyvgart [29%] versus and nasopharyngitis (Vyvgart [12%] versus placebo [18%]). In addition, 4 (5%) Vyvgart-treated individuals and 7 (8%) individuals in the placebo group had a serious adverse event; 3 individuals in each treatment group (4%) discontinued treatment during the study. There were no deaths.

Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc)

Vyvgart Hytrulo is a first-in-class neonatal F c receptor blocker, which is administered as subcutaneous (SC) injection that is approved for gMG by the FDA. It contains efgartigimod alfa, a human immunoglobulin G1 (IgG1) antibody fragment that binds the neonatal Fc receptor (FcRn), keeping antibodies in circulation and preventing FcRn from recycling IgG back into the blood. It also contains recombinant human hyaluronidase PH20, which is Halozyme Therapeutics' Enhanced drug delivery technology that facilitates the SC delivery. The safety and efficacy of Vyvgart Hytrulo was evaluated in a phase 3, randomized, multicenter, open-label, parallel group bridging study to the phase 3 ADAPT study. Individuals were randomized 1:1 to receive Vyvgart Hytrulo or Vyvgart once a week for four weeks. The primary efficacy endpoint was to compare the mean IgG reduction between two groups. At the end of the treatment period, the mean total IgG reduction was 66.6% in the Vyvgart group compared to 62.2% in the Vyvgart group, with p-value < 0.0001. Similar responses were found in the Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG). Also, the safety profile of Vyvgart was similar to Vyvgart Hytrulo other than injection site reactions, which were higher in the Vyvgart Hytrulo group.

Rystiggo (rozanolixizumab-noli)

Rystiggo, administered as a subcutaneous (SC) infusion, is a humanized immunoglobulin G4 monoclonal antibody that binds to neonatal Fc receptor (FcRn), which reduces the levels of circulating IgG. It is FDA-approved for the treatment of generalized myasthenia gravis (gMG) in adult individuals who are anti-AChR or anti-MuSK Ab+. The efficacy of Rystiggo for the treatment of gMG in adults who are anti-AChR Ab+ or anti-MuSK Ab+ was established in the Phase 3 MycarinG trial (Study 1; NCT03971422), a multicenter, randomized, double-blind, placebo-controlled study. The study included a 4-week screening period and a 6-week treatment period, followed by 8 weeks of observation. During the treatment period, Rystiggo or placebo were administered as an SC infusion once a week for 6 weeks. In the MycarinG study, 200 individuals were randomly assigned (1:1:1) to receive SC infusions of Rystiggo 7 mg/kg, Rystiggo 10 mg/kg, or placebo once a week for 6 weeks. Treatment with Rystiggo resulted in a greater reduction in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score at Day 43 than placebo (−3.4 versus −0.8 points). The most common adverse reactions reported in ≥10% of individuals receiving Rystiggo were headache, infections, diarrhea, pyrexia, hypersensitivity reactions, and nausea.

Graft versus Host Disease

Graft-versus-host disease (GVHD) is a potentially fatal complication following allogeneic hematopoietic stem cell transplantation (HSCT) and occurs when immune cells transplanted from a non-identical donor (graft) recognize the transplant recipient (host) as foreign. This initiates an immune reaction, causing damage across different organs and tissues. Acute graft-versus-host disease (aGVHD) classically presents within 100 days of HSCT (usually 2 to 3 weeks post-transplant) and primarily affects the skin, liver, and gastrointestinal (GI) tract. This marker of 100 days is not absolute; some individuals may experience persistent, recurrent, or late-onset aGVHD >100 days after HSCT. Individuals can experience clinical manifestations of aGVHD such as rash, persistent nausea and vomiting, abdominal cramping, and diarrhea. It is estimated that there are approximately 10,000 allogeneic HSCTs performed in the United States every year. Despite the use of current prophylactic regimens, aGVHD occurs in 20% to 80% of HSCT individuals. Even in fully human leukocyte antigen (HLA)–matched (preferred donor source) allogeneic HSCT, the incidence of aGVHD is estimated at about 30% to 50%. The overall survival rate of individuals has improved over the past 2 decades with new advances in technology and antiinfectives. The overall 5-year survival rate in aGVHD individuals is now estimated to be up to 72%. Individuals with aGVHD usually die due to infection or severe GI complications, which are usually resistant to steroid therapy.

Orencia (abatacept)

Orencia is an immunomodulator that inhibits T-cell activation by binding to CD80 and CD86 on antigen-presenting cells; therefore, it can block the signaling processes that would otherwise induce T cells to attack the host. Orencia was studied in acute Graft Versus Host Disease (GVHD) in 2 phase 2 studies: GVHD-1 and GVHD-2. GVHD-1 was a Phase 2, multicenter, 2-cohort clinical trial of 186 individuals ≥6 years of age who underwent HSCT from a matched unrelated donor and received Orencia (or placebo) on Days −1, 5, 14, and 28 in combination with a calcineurin inhibitor (e.g. cyclosporine or tacrolimus) on Day −2 through at least Day 100 and methotrexate on Days 1, 3, 6, and 11. Grade III-IV aGVHD free survival rate was 87% in the Orencia arm and 75% in the placebo arm. The rate of grade II-IV aGVHD free survival was 50% in the Orencia arm and 32% in the placebo arm. Overall survival rate was 97% in the Orencia arm versus 84% in the placebo arm.

GVHD-2, the second study supporting Orencia's approval in aGVHD, used real-world data from the Center for International Blood and Marrow Transplant Research (CIBMTR). This observational study included individuals ≥6 years of age who underwent HSCT from a 1 allele–mismatched unrelated donor between 2011 and 2018 and analyzed the outcomes of individuals who had received Orencia in combination with CNI and methotrexate (n = 54) versus individuals who received CNI and methotrexate alone (n = 162) for the prophylaxis of aGVHD. Forty-two individuals from the GVHD-1 study were included in the Orencia group in the GVHD-2 study. Efficacy was established based on overall survival at Day 180 post-transplant; the overall survival rate at Day 180 in the Orencia group was 98% (95% confidence interval [CI]: 78%, 100%) versus 75% (95% CI: 67%, 82%) in the comparator group (P = 0.0028). Efficacy for Orencia was established based on overall survival and moderate GFS (grade II–IV) results. Orencia did not significantly improve severe GFS (grade III–IV) in the GVHD-1 trial. However, overall survival rates were similar between the GVHD-1 trial and the real-world data analysis from CIBMTR.

n the GVHD-1 study, serious adverse reactions reported up to Day 225 post-transplant included fever (20%), pneumonia (8%), acute kidney injury (7%), diarrhea (6%), hypoxia (5%), and nausea (5%). Common adverse reactions included anemia, hypertension, cytomegalovirus (CMV) reactivation/infection, fever, pneumonia, nosebleed, decrease in CD4 lymphocytes, hypermagnesemia, and acute kidney injury. Individuals receiving Orencia should be monitored for Epstein-Barr virus reactivation before starting treatment and for 6 months post-transplant and CMV infection/reinfection for 6 months post-transplant.

Rezurock (belumosudil)

Rezurock is a rho-associated, coiled-coil kinase 2 (ROCK2) inhibitor. ROCK2 is a signaling pathway that modulates inflammatory response and fibrotic processes. By inhibiting ROCK2, Rezurock is thought to restore immune homeostasis and reduce fibrosis in affected organs. Rezurock was approved based on the results of the Phase 2 randomized, multicenter ROCKstar clinical trial, which enrolled individuals ≥12 years of age with chronic graft versus host disease who had received 2–5 previous lines of systemic therapy (including Imbruvica and Jakafi). The primary endpoint of overall response rate was met by 75% of individuals receiving Rezurock 200 mg once daily and was consistent across all organ systems; 69% (n = 45) of individuals displayed a partial response and 6% (n = 4) displayed a complete response. Overall, Rezurock was well-tolerated with adverse effects similar to corticosteroids and other immunosuppressants.

Primary Immunoglobulin A nephropathy (IgAN)

Immunoglobulin A nephropathy (IgAN) is an autoimmune kidney disease where immunoglobulin A deposits in the glomerular mesangium of the kidneys and attacks the glomeruli. This diminishes the kidney's capacity to filter, resulting in the leakage of blood and protein into the urine. Over many years, the damage may progress slowly, leading to scarring of the nephrons. Eventually IgA nephropathy can lead to end-stage renal disease (ESRD). Individuals can experience clinical manifestations of IgAN such as hematuria with or without proteinuria, acute kidney injury, and rapidly progressive glomerulonephritis. There are approximately 150,000 people affected with IgAN in the United States. The management of primary IgAN includes supportive care such as lifestyle modifications, reducing blood pressure to an optimal level, reducing proteinuria to an optimal level through renin-angiotensin system inhibition, and immunosuppressive therapy.

Filspari (sparsentan)

Filspari is a dual-acting angiotensin II type 1 (AT_1R) and endothelin type A (ET_AR) receptor antagonist that selectively blocks the action of two vasoconstrictor and mitogenic agents to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression. Endothelin-1 and angiotensin II are believed to participate in the pathogenesis of immunoglobulin A nephropathy (IgAN) via the ET_AR and AT_1R pathway. The approval of Filspari for IgAN has been granted under the accelerated approval pathway due to observed reduction in proteinuria.

PROTECT study was randomized, Double-blind, parallel-group, multicenter, active-control study to determine the efficacy and safety of sparsentan compared to irbesartan in the treatment of IgAN. This study included 404 individuals ≥18 years of age with persistent proteinuria (total urine protein ≥ 1.0 g/ day despite being on maximized stable dose of RAS inhibitor treatment (≥ 50% of maximum labeled dose). These individuals were randomized 1:1 to receive Filspari 400 mg once daily following 200 mg once daily for 14 days or irbesartan 300 mg once daily dose following 150 mg once daily for 14 days. The trial protocol allowed for the initiation of rescue immunosuppressive treatment at the investigator's discretion. However, the usage of SGLT2 inhibitors was prohibited during the trial. The primary endpoint of the study was the change, relative to baseline, in urine protein/creatinine ratio (UPCR) at week 36. Following a 36-week treatment period, individuals in the sparsentan group exhibited a mean reduction in proteinuria of 49.8% from baseline, while individuals in the irbesartan treatment group demonstrated a mean reduction in proteinuria of 15.1% from baseline. The secondary endpoint was overall change in eGFR from baseline, change in eGFR over 104-week period and change in eGFR over a 52-week period.

Sparsentan was overall well tolerated. Most common adverse events were peripheral edema, dizziness, hypotension, anemia, and hyperkalemia. An increase in ALT/AST level of at three times the upper limit of normal was observed in 2.5% of individuals in the clinical trial, and evidence of fetal harm was detected in animal reproduction studies. There are two specific reasons have resulted in Filspari being available only through the Filspari REMS (Risk Evaluation and Mitigation Strategy) program.

Tarpeyo (budesonide)

Tarpeyo was approved based on the results from the first part of the Phase 3 NefIgArd study (NCT03643965), a randomized, double-blind trial in adult patients with biopsy-verified IgAN, reduced kidney function (estimated glomerular filtration rate [eGFR] ≥35 mL/min/1.73 m2), and proteinuria (≥1 g/day or urine protein to creatinine ratio [UPCR] ≥0.8) who were receiving a stable dose of a maximally tolerated renin-angiotensin system (RAS) inhibitor therapy, either angiotensin-covering enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In Part A of the study, individuals were randomized to receive Tarpeyo 16 mg once daily (n = 97) or placebo (n = 102) for 9 months, followed by a 2-week taper of either Tarpeyo 8 mg once daily or placebo. The primary endpoint of the study was percentage reduction in UPCR from baseline. At 9 months, a 34% reduction in UPCR was observed in individuals receiving Tarpeyo versus a 5% reduction in the placebo group (31% [95% confidence interval, 16% to 42%]; P = 0.0001). Adverse effects were mild or moderate in severity in Part A of the NefIgArd study. Common

adverse reactions (>5%) included hypertension (16%), peripheral edema (14%), muscle spasms (13%), acne (11%), dermatitis (7%), weight increase (7%), dyspnea (6%), and face edema (6%).

2019 Update

Reviewed prescribing information and conducted literature search for all drugs listed in policy. Updated criteria for Benlysta (belimumab) IV for use in individuals aged 5 years and older.

2020 Update

Reviewed prescribing information for all drugs listed in policy and conducted a literature search on the management of hidradenitis suppurativa, pyoderma gangrenosum, and systemic lupus erythematosus. No new evidence found that would change this policy. Added links to the ACR, EULAR/ACR, and SLICC criteria.

2021 Update

Reviewed prescribing information for all drugs listed in policy and conducted a literature search on the management of pyoderma gangrenosum, giant cell arteritis, and neuromyelitis optica spectrum disorder. No new evidence found that would change this policy. Added Arcalyst (rilonacept) to policy for the FDA-approved indications which is treatment of cryopyrin-associated periodic syndromes (CAPS), maintenance of remission of deficiency of interleukin-1 receptor antagonist (DIRA), and treatment of recurrent pericarditis (RP). Updated Ilaris (canakinumab) criteria adding requirement the drug is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist which brings drug criteria in alignment with Kineret (anakinra) and Arcalyst (rilonacept) for the management of CAPS. Updated the investigational table adding restrictions on combination therapy and for drug quantities that exceed the FDA labeled dosing for condition.

2022 Update

Reviewed prescribing information and conducted literature search for all drugs listed in policy. No new evidence found that would change this policy. Added criteria for Vyvgart for the treatment of generalized myasthenia gravis (gMG) in adult individuals who are anti-

acetylcholine receptor (AChR) antibody positive. Added criteria for Orencia for the prophylaxis of acute graft versus host disease (aGVHD).

2023 Update

Reviewed prescribing information and conducted literature search for all drugs listed in policy. No new evidence found that would change this policy. Added criteria for Filspari for the treatment of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression. Added criteria for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) for the treatment of generalized myasthenia gravis (gMG) in adult individuals who are anti-acetylcholine receptor (AChR) antibody positive. Added coverage for the biosimilars Hyrimoz LCF (adalimumab-adaz) SC, Abrilada (adalimumab-afzb) SC, Hulio ((adalimumab-fkjp) SC, Yusimry (adalimumab-aqvh) SC, Hadlima (adalimumab-bwwd) SC, and Yuflyma (adalimumab-aaty) SC for the treatment of HS, PG, and uveitis as non-preferred products and with the identical coverage criteria as Amjevita (adalimumab-atto) [NDCs starting with 72511]. Added coverage for Cyltezo LCF (adalimumab-adbm), Hyrimoz HCF (adalimumab-adaz) and Adalimumab-adaz HCF (Sandoz – unbranded) SC for the treatment of HS, PG, and uveitis as preferred products and with the identical coverage criteria as Amjevita (adalimumab-atto) [NDCs starting with 55513]. Moved Avsola to 1st line (preferred) with the effective date of 01/01/2024. Added Avsola to the list of preferred infliximab products to be tried and failed prior to non-preferred infliximab products with the effective date of 01/01/2024. Moved Inflectra to 2nd line (non-preferred) infliximab products with the effective date of 01/01/2024. Removed Inflectra from the list of preferred infliximab products to be tried and failed prior to trying non-preferred infliximab products with the effective date of 01/01/2024. Added Humira biosimilars Adalimumab-fkjp (Biocon-unbranded) and Idacio (adalimumab-aacf) as non-preferred products with similar criteria as Amjevita (adalimumab-atto) [NDCs starting with 72511]. Updated criteria for Actemra for the treatment of CRS to require documentation confirming the diagnosis. Added criteria for Rystiggo (rozanolixizumab-noli) for the treatment of gMG. Updated Amjevita [NDCs starting with 55513] to a non-preferred product effective January 1, 2024. Added Hyrimoz (Cordavis) [NDCs starting with 83457] and adalimumab-aacf (Idacio) as a non-preferred product effective January 1, 2024. Added adalimumab-adbm (Cyltezo unbranded) as a preferred product effective January 1, 2024. Updated Hyrimoz LCF (Sandoz) from a non-preferred to a preferred product effective January 1, 2024.

2024 Update

Reviewed prescribing information and conducted literature search for all drugs listed in policy. Added coverage criteria for Cosentyx (secukinumab) for the treatment of adults with moderate to severe hidradenitis suppurativa. Updated Vyvgart (efgartigimod alfa-fcab) criteria to require that medication is not being used concurrently with Vyvgart Hytrulo, Rystiggo, Soliris, Ultomiris, or Zilbrysq. Updated Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) criteria to require that medication is not being used concurrently with Vyvgart, Rystiggo, Soliris, Ultomiris, or Zilbrysq. Added coverage criteria for Tarpeyo (budesonide) for the treatment of adults with primary immunoglobulin A nephropathy (IgAN). Added coverage criteria for Rezurock (belumosudil) for the treatment of chronic graft versus host disease. Updated coverage criteria for Cosentyx (secukinumab) and removed adalimumab step therapy requirement for the treatment of adults with moderate to severe hidradenitis suppurativa. Added Humira (adalimumab) (Cordavis) [NDCs starting with 83457] as a non-preferred product. Added adalimumab-aaty (Yuflyma unbranded) as a non-preferred product. Added Simlandi (adalimumab-ryvk) and adalimumab-ryvk (Simlandi unbranded) as preferred products. Updated Lupkynis (voclosporin) coverage criteria to clarify that the requirement is for Lupkynis (voclosporin) to be used in combination with mycophenolate, cyclophosphamide, azathioprine, or an immunosuppressant and a corticosteroid. Updated Benlysta (belimumab) SC for systemic lupus erythematosus (SLE) coverage criteria to include coverage of pediatric individuals 5 years and older. Updated non-preferred adalimumab coverage criteria to require trial and treatment failure with all preferred adalimumab products. Updated Rystiggo (rozanolixizumab-noli) coverage criteria to require that the medication not being used concurrently with Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Zilbrysq (zilucoplan).

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37. Tarpeyo (budesonide). Prescribing Information. Calliditas Therapeutics, New York, NY. Revised December 2023.

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History

Date	Comments
07/01/16	New policy approved June 14, 2016, add to Prescription Drug section. Policy information on drug treatment for miscellaneous autoimmune diseases extracted from 5.01.550. Medical necessity review criteria for site of service IV therapy added.
10/01/16	Interim Update, approved September 13, 2016: inclusion of a new indication for Humira; changing criteria for Benlysta (defining “adequate” trial of previous therapies).
11/01/16	Interim review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages. Coding update, added HCPCS Q5102.
07/01/17	Annual review, approved June 13, 2017. Added coverage criteria for Actemra in the setting of giant cell arteritis, added HCPCS code J3262. Formatting update; added hyperlinks to Medical Necessity criteria sections.
08/15/17	Interim Review, approved August 15, 2017. Added Benlysta SC.

Date	Comments
09/01/17	Interim review, approved August 15, 2017. Added Infliximab-abda (Renflexis) to coverage criteria and coding section. Clarified pyoderma gangrenosum first-line/second-line treatment.
11/01/17	Interim Review, approved October 3, 2017. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug. Removed HCPCS codes J3490 and J3590.
02/14/18	Interim Review, approved February 13, 2018. Update hospital-based outpatient coverage from 30 days to 90 days.
04/01/18	Coding update: added new HCPCS codes Q5103 and Q5104 (effective 4/1/18), noted that Q5102 terminated 4/1/18.
07/01/18	Annual Review, approved June 22, 2018. Dosage and quantity limit prescribing table was removed. Two related medical policies were added in related medical policy section.
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
12/01/18	Interim Review, approved November 21, 2018. Updated pediatric indications for Humira: uveitis and hidradenitis.
01/01/19	Coding update, added new HCPCS code Q5109 (new code effective 1/1/19).
04/01/19	Coding update: removed HCPCS code Q5102 as it terminated 4/1/18.
08/01/19	Annual Review, approved July 25, 2019. Updated criteria for Benlysta (belimumab) IV. Removed HCPCS code J9310.
09/01/19	Interim Review, approved August 22, 2019. Added criteria for Otezla (apremilast) for Bechet's Disease.
01/01/20	Interim Review, approved December 17, 2019, effective for dates of service on or after April 3, 2020, following provider notification. Added Ruxience (rituximab-pvvr) with Rituxan.
10/01/20	Annual Review, approved September 8, 2020. Added coverage criteria for Uplizna (inebilizumab-cdon) for the treatment of NMOSD. Added coverage criteria for Enspryng (satralizumab-mwge) for the treatment of NMOSD. Added Avsola (infliximab-axxq) as a second-line agent for the treatment pyoderma gangrenosum along with site-of-service requirement. Added HCPCS codes Q5121 and J3590 Effective for dates of service on or after January 1, 2021, after provider notification: Added Ilaris (canakinumab) to policy with coverage criteria for periodic fever syndromes and Still's disease. Added HCPCS code J0638.
01/01/21	Interim Review, approved December 17, 2020. Added coverage criteria for Actemra (tocilizumab) for the treatment of cytokine release syndrome. Added HCPCS code J1823.

Date	Comments
02/01/21	Interim Review, approved January 12, 2021. Added coverage criteria for Benlysta (belimumab) for the treatment of lupus nephritis. Removed HCPCS J0717 and Q5109.
06/01/21	Interim Review, approved May 11, 2021. Added Kineret (anakinra) for the treatment of cryopyrin-associated periodic syndromes and the deficiency of interleukin-1 receptor antagonist. Added Lupkynis (voclosporin) for the treatment of lupus nephritis. Updated Benlysta (belimumab) criteria for the treatment of lupus nephritis removing prior use of Benlysta in the prior 12 months and adding restriction on combination therapy with Lupkynis.
09/01/21	Annual Review, approved August 10, 2021. Updated Ilaris (canakinumab) criteria adding requirement the drug is prescribed by or in consultation with a rheumatologist, geneticist, or dermatologist. Updated the investigational table adding restrictions on combination therapy and for drug quantities that exceed the FDA labeled dosing for condition. Added Arcalyst (rilonacept) for the treatment of DIRA, CAPS, and RP. Coverage criteria for Arcalyst (rilonacept) (HCPCS code J2793) becomes effective for dates of service on or after December 2, 2021, following 90-day provider notification.
11/01/21	Interim Review, approved October 12, 2021. Added coverage criteria for Saphnelo (anifrolumab-fnia) for the treatment of adult individuals with SLE. Updated Benlysta (belimumab) criteria regarding concurrent use with Saphnelo (anifrolumab-fnia) for the treatment of SLE. Added site of service review for Uplizna (inebilizumab-cdon) for dates of service on or after February 4, 2022.
01/01/22	Interim Review, approved December 14, 2021. Updated Humira criteria for the treatment of hidradenitis suppurativa to include individual has tried at least one other therapy and prescriber specialty. Updated Humira criteria for the treatment of uveitis to include individual has tried at least one other therapy and prescriber specialty. For pyoderma gangrenosum added prescriber specialty to Humira, Enbrel, Remicade, Inflectra, Renflexis, and Avsola. Updated Actemra criteria for the treatment of giant cell arteritis to include individual has tried at least one other therapy and prescriber specialty. Updated Otezla criteria for the treatment of Behcet's Disease to include individual has tried at least one other therapy and prescriber specialty. Added HCPCS code C9086.
04/01/22	Annual Review, approved March 8, 2022. Added criteria for Vyvgart for the treatment of generalized myasthenia gravis in adult individuals who are AChR antibody positive. Added criteria for Orencia for the prophylaxis of acute graft versus host disease. Added HCPCS code J0129. Added term date to HCPC code C9086. Added code J0491.
06/01/22	Interim Review, approved May 10, 2022. Added Infliximab (Janssen – unbranded) to policy with identical site-of-service requirements and coverage criteria as brand Remicade (infliximab) for the treatment of pyoderma gangrenosum. Moved Inflectra (infliximab-dyyb) to a first-line TNF-α antagonists for the treatment of pyoderma gangrenosum. Updated coverage criteria for Renflexis (infliximab-abda) and Avsola (infliximab-axxq) for the treatment of pyoderma gangrenosum to require the individual has had an inadequate response or intolerance to Infliximab (Janssen – unbranded), Inflectra (infliximab-dyyb), or Remicade (infliximab).

Date	Comments
07/01/22	Coding update. Added HCPCS code J9332.
10/01/22	Interim Review, approved September 13, 2022. Updated Benlysta IV and Benlysta SC criteria for the treatment of SLE to require the drug is being used as add-on-therapy following standard induction. Updated Benlysta IV criteria for the treatment of active lupus nephritis from 18 years of age or older to 5 years of age or older. Changed the wording from "patient" to "individual" throughout the policy for standardization.
02/01/23	Interim Review, approved January 10, 2023. Added coverage for the biosimilar Amjevita (adalimumab-atto) for the treatment of hidradenitis suppurativa, pyoderma gangrenosum, and uveitis with the identical coverage criteria as Humira (adalimumab). Added HCPC code J0135. Added Amjevita to HCPC code J3590.
04/01/23	Interim Review, approved March 14, 2023. Added criteria for Filspari (sparsentan) for the treatment of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.
08/01/23	Annual Review, approved at MPC, July 11, 2023. Reviewed prescribing information for all drugs in the policy. Added criteria for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) for the treatment of generalized myasthenia gravis (gMG) in adult individuals who are anti-acetylcholine receptor (AChR) antibody positive. Added coverage for the biosimilars Hyrimoz LCF (adalimumab-adaz) SC, Abrilada (adalimumab-afzb) SC, Hulio ((adalimumab-fkjp) SC, Yusimry (adalimumab-aqvh) SC, Hadlima (adalimumab-bwwd) SC, and Yuflyma (adalimumab-aaty) SC for the treatment of HS, PG, and uveitis as non-preferred products and with the identical coverage criteria as Amjevita (adalimumab-atto) [NDCs starting with 72511]. Added coverage for Cyltezo LCF (adalimumab-adbm), Hyrimoz HCF (adalimumab-adaz) and Adalimumab-adaz HCF (Sandoz – unbranded) SC for the treatment of HS, PG, and uveitis as preferred products and with the identical coverage criteria as Amjevita (adalimumab-atto) [NDCs starting with 55513]. Added Cyltezo, Hyrimoz HCF, Adalimumab-adaz HCF (Sandoz – unbranded), Abrilada, Hadlima, Hulio, Hyrimoz LCF, Yuflyma and Yusimry to code J3590.
09/01/23	Interim Review, approved August 8, 2023. The following policy changes are effective September 1, 2023: added Humira biosimilars Adalimumab-fkjp (Biocon-unbranded) and Idacio (adalimumab-aacf) as non-preferred products with similar criteria as Amjevita (adalimumab-atto) [NDCs starting with 72511]. The following policy changes are effective January 1, 2024 following 90-day provider notification due to changes in the preferred medical benefit drugs: moved Avsola to 1st line (preferred); added Avsola to the list of preferred infliximab products to be tried and failed prior to non-preferred infliximab products; moved Inflectra to 2nd line (non-preferred) infliximab products; removed Inflectra from the list of preferred infliximab products to be tried and failed prior to trying non-preferred infliximab products.
11/01/23	Interim Review, approved October 10, 2023. Updated criteria for Actemra for the treatment of CRS to require documentation confirming the diagnosis.

Date	Comments
12/01/23	Interim Review, approved November 14, 2023. Added criteria for Rystiggo (rozanolixizumab-noli) for the treatment of gMG. Added drug name Rystiggo to HCPCS code J3590.
01/01/24	Interim Review, approved December 12, 2023. Updated Amjevita [NDCs starting with 55513] to a non-preferred product. Added Hyrimoz (Cordavis) [NDCs starting with 83457] and adalimumab-aacf (Idacio) as a non-preferred product. Added adalimumab-adbm (Cyltezo unbranded) as a preferred product. Updated Hyrimoz LCF (Sandoz) from a non-preferred to a preferred product. Added new HCPCS codes J9333 and J9334.
02/01/24	Annual Review, approved January 9, 2024. Added coverage criteria for Cosentyx (secukinumab) for the treatment of adults with moderate to severe hidradenitis suppurativa. Updated Vyvgart (efgartigimod alfa-fcab) criteria to require that medication is not being used concurrently with Vyvgart Hytrulo, Rystiggo, Soliris, Ultomiris, or Zilbrysq. Updated Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) criteria to require that medication is not being used concurrently with Vyvgart, Rystiggo, Soliris, Ultomiris, or Zilbrysq. Added coverage criteria for Tarpeyo (budesonide) for the treatment of adults with primary immunoglobulin A nephropathy (IgAN). Added coverage criteria for Rezurock (belumosudil) for the treatment of chronic graft versus host disease.
03/01/24	Interim Review approved February 13, 2024. Updated coverage criteria for Cosentyx (secukinumab) and removed adalimumab step therapy requirement for the treatment of adults with moderate to severe hidradenitis suppurativa.
05/01/24	Interim Review, approved April 9, 2024. Added Humira (adalimumab) (Cordavis) [NDCs starting with 83457] as a non-preferred product.
07/01/24	Interim Review, approved June 11, 2024. Added adalimumab-aaty (Yuflyma unbranded) as a non-preferred product. Added Simlandi (adalimumab-ryvk) and adalimumab-ryvk (Simlandi unbranded) as preferred products. Updated Lupkynis (voclosporin) coverage criteria to clarify that the requirement is for Lupkynis (voclosporin) to be used in combination with mycophenolate, cyclophosphamide, azathioprine, or an immunosuppressant and a corticosteroid. Updated Benlysta (belimumab) SC for systemic lupus erythematosus (SLE) coverage criteria to include coverage of pediatric individuals 5 years and older. Updated non-preferred adalimumab coverage criteria to require trial and treatment failure with all preferred adalimumab products. Updated Rystiggo (rozanolixizumab-noli) coverage criteria to require that the medication not being used concurrently with Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Zilbrysq (zilucoplan). Added drug name Simlandi to HCPCS code J3590.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and

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Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY：711）。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 800-722-1471 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

MO LOU SILAFIA: Afai e te tautala Gagana fa'a Sāmoa, o loo iai auaunaga fesoasoan, e fai fua e leai se totogi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັຽຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 800-722-1471 (TTY: 711).

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。800-722-1471 （TTY:711）まで、お電話にてご連絡ください。

PAKDAAR: Nu saritaem ti Ilocano, ti serbisyo para ti baddang ti lengguahe nga awanan bayadna, ket sidadaan para kenyam. Awagan ti 800-722-1471 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 800-722-1471 (телетайп: 711).

ប្រយ័ត្ន៖ បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតឈ្នួល គឺអាចមានសំរាប់បំរើអ្នក។ ចូរ ទូរស័ព្ទ 800-722-1471 (TTY: 711)។

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው: 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 800-722-1471 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-722-1471 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 800-722-1471 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

เรียน: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 800-722-1471 (TTY: 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 800-722-1471 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 800-722-1471 (TTY: 711).

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 800-722-1471 (ATS : 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 800-722-1471 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 800-722-1471 (TTY: 711).

توجه: اگر به زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 800-722-1471 (TTY: 711) تماس بگیرید.

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