LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.563

Pharmacotherapy of Inflammatory Bowel Disorder

Effective Date: **Jan. 3, 2025***	RELATED MEDICAL POLICIES:
Last Revised: Oct. 8, 2024	11.01.523 Site of Service: Infusion Drugs and Biologic Agents
Replaces: Extracted from 5.01.550	
*Click here to view current policy.	

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

Inflammatory bowel disorder describes several diseases where the lining of the digestive tract becomes chronically inflamed. Inflammation may cause internal sores or ulcers in the gut and symptoms of abdominal pain, cramping, diarrhea, bleeding, feeling tired, and weight loss. The two most common diseases include Crohn's disease (CD) and ulcerative colitis (UC). In Crohn's disease the entire digestive tract may be involved. In ulcerative colitis the disease is limited to the colon or large bowel only. Both disorders can be chronic; so far there is not a cure for either. However, there are many different medications that can be used to treat these disorders. This policy describes treatment for the most common inflammatory bowel disease and which drugs may need pre-approval.

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)
- Entyvio (vedolizumab) IV
- Inflectra (infliximab-dyyb)
- Infliximab (Janssen – unbranded)
- Remicade (infliximab)
- Renflexis (infliximab-abda)
- Skyrizi (risankizumab-rzaa) IV
- Stelara (ustekinumab) IV
- Tyruko (natalizumab-sztn)
- Tysabri (natalizumab)

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

Crohn's Disease **Ulcerative Colitis** **Site of Service Infusion**

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* **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

Site of Service Administration	Medical Necessity
	• 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.**

Medical and Biological Agents

Please note that claims billed for the drugs described in this policy that are administered via an intravenous route (IV) must be processed through a medical benefit only (not pharmacy).

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

Step therapy tiers are listed below, please refer to the Policy section for details:

Crohn's Disease				
First-line Agents				
TNF-α Inhibitors (first-line)	**IL-12/23 Inhibitor (first-line)**	**IL-23 Inhibitor (first-line)**	**α-4 Integrin Inhibitor (first-line)**	**Janus Kinase Inhibitors (first-line)**
Inflectra (IV) Infliximab (Janssen – unbranded) (IV) Remicade (IV)	Stelara (IV) (induction)	Skyrizi (IV) (induction)	Entyvio (IV)	Rinvoq (oral)

Crohn's Disease				
Cyltezo (SC) Humira (AbbVie) [NDCs starting with 00074] (SC) Simlandi (adalimumab-ryvk) (SC) Adalimumab-adaz (Hyrimoz unbranded) (SC) Adalimumab-adbm (Cyltezo unbranded) (SC) Adalimumab-ryvk (Simlandi unbranded) (SC) Zymfentra (SC)	Stelara (SC) (use after IV only)	Skyrizi (SC) (use after IV only)		
Second-line Agents				
TNF-α Inhibitors (second-line)		**α-4 Integrin Inhibitor (second-line)**		
Avsola (IV) Renflexis (IV)		Entyvio (SC)		
Abrilada (SC) Adalimumab-aacf (Idacio unbranded) (SC) Adalimumab-aaty (Yuflyma unbranded) (SC) Adalimumab-fkjp (Hulio unbranded) (SC) Amjevita (SC) Hadlima (SC) Hulio (SC) Humira (Cordavis) [NDCs starting with 83457] (SC) Hyrimoz (SC) Idacio (SC) Yuflyma (SC) Yusimry (SC) Cimzia (SC)		Tyruko (IV) Tysabri (IV)		

Drug	Medical Necessity for Crohn's Disease
First-line TNF-α Antagonists	
• **Cyltezo (adalimumab-adbm) SC**	**Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), and adalimumab-ryvk (Simlandi**

Drug	Medical Necessity for Crohn's Disease
• **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] SC** • **Simlandi (adalimumab-ryvk) SC** • **Adalimumab-adaz (Hyrimoz unbranded) SC** • **Adalimumab-adbm (Cyltezo unbranded) SC** • **Adalimumab-ryvk (Simlandi unbranded) SC**	**unbranded) may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Medication is being prescribed by or in consultation with a gastroenterologist **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR**

Drug	Medical Necessity for Crohn's Disease

	• Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence)
	AND
	• Has had a trial and treatment failure with one of the following:[1]
	  ○ A preferred adalimumab product: Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)
	  ○ Stelara (ustekinumab) SC
	  ○ Skyrizi (risankizumab-rzaa) SC on-body injector
	  ○ Zymfentra (infliximab-dyyb)
	AND
	• Medication is being prescribed by or in consultation with a gastroenterologist
	
	[1]Note: Only applies to individuals not previously treated with requested therapy

Zymfentra (infliximab-dyyb) SC	**Zymfentra (infliximab-dyyb) may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Has received an intravenous infliximab induction regimen (e.g., Remicade, Avsola, Inflectra, or Renflexis) **AND**

Drug	Medical Necessity for Crohn's Disease
	• Medication is being prescribed by or in consultation with a gastroenterologist
• **Inflectra (infliximab-dyyb) IV** • **Infliximab (Janssen – unbranded) IV** • **Remicade (infliximab) IV**	**Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), and Remicade (infliximab) are subject to review for site of service administration.** **Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), and Remicade (infliximab) may be considered medically necessary for the treatment of Crohn's disease when:** • The individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • The medication is prescribed by or in consultation with a gastroenterologist
First-line α-4 Integrin Inhibitors	
Entyvio (vedolizumab) IV	**Entyvio (vedolizumab) IV is subject to review for site of service administration.** **Entyvio (vedolizumab) IV may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication

Drug	Medical Necessity for Crohn's Disease
	OR • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Entyvio (vedolizumab) IV is being prescribed by or in consultation with a gastroenterologist
First-line IL-12 and IL-23 Antagonist	
• **Stelara (ustekinumab) IV** • **Stelara (ustekinumab) SC**	**Stelara (ustekinumab) IV is subject to review for site of service administration.** **Stelara (ustekinumab) IV may be considered medically necessary for the treatment of moderately to severely active Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, or budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND**

Drug	Medical Necessity for Crohn's Disease
	• Stelara (ustekinumab) IV is being prescribed by or in consultation with a gastroenterologist **AND** • Stelara (ustekinumab) IV is used for only a one-time induction dose **Stelara (ustekinumab) SC may be considered medically necessary for the treatment of moderately to severely active Crohn's disease when:** • Individual has received a single induction dose with Stelara (ustekinumab) IV **AND** • Has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, or budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Stelara (ustekinumab) SC is being prescribed by or in consultation with a gastroenterologist
First-line IL-23 Antagonist	
• **Skyrizi (risankizumab-rzaa) IV** • **Skyrizi (risankizumab-rzaa) SC on-body injector**	**Skyrizi (risankizumab-rzaa) IV is subject to review for site of service administration.** **Skyrizi (risankizumab-rzaa) IV may be considered medically necessary for the treatment of moderately to severely active Crohn's disease when:**

Drug	Medical Necessity for Crohn's Disease
	• Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, or budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Skyrizi (risankizumab-rzaa) IV is being prescribed by or in consultation with a gastroenterologist **AND** • Skyrizi (risankizumab-rzaa) IV is used only for induction therapy (administered at Week 0, Week 4, and Week 8 for a total of 3 IV infusions) **Skyrizi (risankizumab-rzaa) SC on-body injector may be considered medically necessary for the treatment of moderately to severely active Crohn's disease when:** • Individual has received induction therapy with Skyrizi (risankizumab-rzaa) IV **AND** • Has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, or budesonide, etc.) or is currently taking a corticosteroid medication **OR** • One other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR**

Drug	Medical Necessity for Crohn's Disease
	• Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Skyrizi (risankizumab-rzaa) SC on-body injector is being prescribed by or in consultation with a gastroenterologist
First-line Janus Kinase (JAK) Inhibitors	
Rinvoq (upadacitinib)	**Rinvoq (upadacitinib) may be considered medically necessary for the treatment of moderately to severely active Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, or budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Has had a trial and treatment failure with one or more TNF blockers **AND** • Rinvoq is being prescribed by or in consultation with a gastroenterologist
Second-line TNF-α Antagonists	
• **Abrilada (adalimumab-afzb) SC** • **Adalimumab-aacf (Idacio unbranded) SC**	**Abrilada (adalimumab-afzb), adalimumab-aacf (Idacio unbranded), adalimumab-aaty (Yuflyma unbranded), adalimumab-fkjp (Hulio unbranded), Amjevita (adalimumab-**

Drug	Medical Necessity for Crohn's Disease

• **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) SC**
• **Idacio (adalimumab-aacf) SC**
• **Yuflyma (adalimumab-aaty) SC**
• **Yusimry (adalimumab-aqvh) SC**
	atto), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Humira (adalimumab) (Cordavis) [NDCs starting with 83457], Hyrimoz (adalimumab-adaz), Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty), and Yusimry (adalimumab-aqvh) may be considered medically necessary for the treatment of Crohn's disease when:
	• Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication
	OR
	• Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.)
	OR
	• Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas
	OR
	• Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence)
	AND
	• Has had a trial and treatment failure with ALL the following:
	  ○ Cyltezo (adalimumab-adbm) OR adalimumab-adbm (Cyltezo unbranded)
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Adalimumab-adaz (Hyrimoz unbranded)
	  ○ Simlandi (adalimumab-ryvk) OR adalimumab-ryvk (Simlandi unbranded)
	AND
	• Medication is being prescribed by or in consultation with a gastroenterologist

• **Cimzia (certolizumab pegol) SC**	**Cimzia (certolizumab pegol) may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication

Drug	Medical Necessity for Crohn's Disease

	OR
	• Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.)
	OR
	• Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas
	OR
	• Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence)
	AND
	• Has had a trial and treatment failure with ONE the following:
	  ○ Cyltezo (adalimumab-adbm)
	  ○ Adalimumab-adbm (Cyltezo unbranded)
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Adalimumab-adaz (Hyrimoz unbranded)
	  ○ Simlandi (adalimumab-ryvk)
	  ○ Adalimumab-ryvk (Simlandi unbranded)
	AND
	• Medication is being prescribed by or in consultation with a gastroenterologist

• **Avsola (infliximab-axxq) IV,** • **Renflexis (infliximab-abda) IV**	**Avsola (infliximab-axxq) and Renflexis (infliximab-abda) are subject to review for site of service administration.** **Avsola (infliximab-axxq) and Renflexis (infliximab-abda) may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR**

Drug	Medical Necessity for Crohn's Disease
	• Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • The individual has had an inadequate response or intolerance to Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), or Remicade (infliximab) **AND** • The medication is prescribed by or in consultation with a gastroenterologist
Second-line α-4 Integrin Inhibitors	
Entyvio (vedolizumab) SC	**Entyvio (vedolizumab) SC may be considered medically necessary for the treatment of adult individuals with Crohn's disease when:** • Individual is aged 18 years and older **AND** • Has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence) **AND** • Entyvio (vedolizumab) SC is being prescribed by or in consultation with a gastroenterologist **AND**

Drug	Medical Necessity for Crohn's Disease

	• Individual has had a trial and treatment failure with TWO of the following:
	  ○ A preferred adalimumab product: Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)
	  ○ Cimzia (certolizumab pegol)
	  ○ Rinvoq (upadacitinib)
	  ○ Stelara (ustekinumab) SC
	  ○ Skyrizi (risankizumab-rzaa) SC on-body injector
	  ○ Zymfentra (infliximab-dyyb)
	AND
	• Has received induction therapy with Entyvio (vedolizumab) IV
	OR
	• Has already started on or is currently undergoing induction therapy with Entyvio (vedolizumab) IV

• **Tyruko (natalizumab-sztn) IV** • **Tysabri (natalizumab) IV**	**Tyruko (natalizumab-sztn) and Tysabri (natalizumab) is subject to review for site of service administration.** **Tyruko (natalizumab-sztn) and Tysabri (natalizumab) may be considered medically necessary for the treatment of Crohn's disease when:** • Individual has tried one corticosteroid (e.g., methylprednisolone, prednisone, prednisolone, dexamethasone, or budesonide, etc.) or is currently taking a corticosteroid medication **OR** • Has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, methotrexate, mesalamine extended-release [Pentasa formulation], etc.) **OR** • Has enterocutaneous (perianal or abdominal) or rectovaginal fistulas **OR** • Has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence)

Drug	Medical Necessity for Crohn's Disease
	AND • Has had a trial and treatment failure with one or more TNF blockers **AND** • The medication is being prescribed by or in consultation with a gastroenterologist

Step therapy tiers are listed below, please refer to the Policy section for details:

Ulcerative Colitis				
First-line Agents				
TNF-α Inhibitors (first-line)	**α -4 Integrin Inhibitor (first-line)**	**IL-12/23 Inhibitor (first-line)**	**IL-23 Inhibitor (first-line)**	**Janus Kinase Inhibitors (first-line)**
Inflectra (IV) Infliximab (Janssen – unbranded) (IV) Remicade (IV)	Entyvio (IV)	Stelara (IV) (induction)	Skyrizi (IV) (induction) Tremfya (IV) (induction)	Rinvoq (oral) Xeljanz (oral) Xeljanz XR (oral)
Cyltezo (SC) Humira (AbbVie) [NDCs starting with 00074] (SC) Simlandi (adalimumab-ryvk) (SC) Adalimumab-adaz (Hyrimoz unbranded) (SC) Adalimumab-adbm (Cyltezo unbranded) (SC) Adalimumab-ryvk (Simlandi unbranded) (SC) Zymfentra (SC)		Stelara (SC) (use after IV only)	Skyrizi (SC) (use after IV only) Tremfya (SC) (use after IV only)	
Second-line Agents				
TNF-α Inhibitors (second-line)	**α -4 Integrin Inhibitor (second-line)**	**IL-23 Inhibitor (second-line)**		**S1P Receptor Modulators**

Ulcerative Colitis			
			(second-line)
Avsola (IV) Renflexis (IV)		Omvoh (IV)	
Abrilada (SC) Adalimumab-aacf (Idacio unbranded) (SC) Adalimumab-aaty (Yuflyma unbranded) (SC) Adalimumab-fkjp (Hulio unbranded) (SC) Amjevita (SC) Hadlima (SC) Hulio (SC) Humira (Cordavis) [NDCs starting with 83457] (SC) Hyrimoz (SC) Idacio (SC) Yuflyma (SC) Yusimry (SC) Simponi (SC)	Entyvio (SC)	Omvoh (SC)	Velsipity (oral) Zeposia (oral)

Drug	Medical Necessity for Ulcerative Colitis
First-line TNF-α Inhibitors	
• **Cyltezo (adalimumab-adbm) SC** • **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] SC** • **Simlandi (adalimumab-ryvk) SC** • **Adalimumab-adaz (Hyrimoz unbranded) SC** • **Adalimumab-adbm (Cyltezo unbranded) SC**	**Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), and adalimumab-ryvk (Simlandi unbranded) may be considered medically necessary for the treatment of ulcerative colitis when:** • Medication is being prescribed by or in consultation with a gastroenterologist **Humira (adalimumab) (AbbVie) [NDCs starting with 00074] may be considered medically necessary for the treatment of ulcerative colitis when:**

Drug	Medical Necessity for Ulcerative Colitis

• **Adalimumab-ryvk (Simlandi unbranded) SC**	• Medication is being prescribed by or in consultation with a gastroenterologist
	AND
	• Individual has had a trial and treatment failure with one of the following:[1]
	  ○ A preferred adalimumab product: Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)
	  ○ Skyrizi (risankizumab-rzaa) SC
	  ○ Stelara (ustekinumab) SC
	  ○ Zymfentra (infliximab-dyyb)
	
	[1]Note: Only applies to individuals not previously treated with requested therapy

Zymfentra (infliximab-dyyb) SC	**Zymfentra (infliximab-dyyb) may be considered medically necessary for the treatment of ulcerative colitis when:** • Individual has received an intravenous infliximab induction regimen (e.g., Remicade, Avsola, Inflectra, or Renflexis) **AND** • Medication is being prescribed by or in consultation with a gastroenterologist
• **Inflectra (infliximab-dyyb) IV** • **Infliximab (Janssen – unbranded) IV** • **Remicade (infliximab) IV**	**Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), and Remicade (infliximab) are subject to review for site of service administration.** **Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), and Remicade (infliximab) may be considered medically necessary for the treatment of ulcerative colitis when:** • The medication is prescribed by or in consultation with a gastroenterologist
First-line α-4 Integrin Inhibitor	
Entyvio (vedolizumab) IV	**Entyvio (vedolizumab) IV is subject to review for site of service administration.**

Drug	Medical Necessity for Ulcerative Colitis
	Entyvio (vedolizumab) IV may be considered medically necessary for the treatment of ulcerative colitis when: • Entyvio (vedolizumab) IV is being prescribed by or in consultation with a gastroenterologist
First-line IL-12 and IL-23 Inhibitor	
• **Stelara (ustekinumab) IV** • **Stelara (ustekinumab) SC**	**Stelara (ustekinumab) IV is subject to review for site of service administration.** **Stelara (ustekinumab) IV may be considered medically necessary for the treatment of ulcerative colitis when:** • Stelara (ustekinumab) IV is being prescribed by or in consultation with a gastroenterologist **AND** • Stelara (ustekinumab) IV is used for only a one-time induction dose **Stelara (ustekinumab) SC may be considered medically necessary for the treatment of ulcerative colitis when:** • Individual has received a single induction dose with Stelara (ustekinumab) IV **AND** • Stelara (ustekinumab) SC is being prescribed by or in consultation with a gastroenterologist
First-line IL-23 Inhibitor	
• **Skyrizi (risankizumab-rzaa) IV** • **Skyrizi (risankizumab-rzaa) SC on-body injector**	**Skyrizi (risankizumab-rzaa) IV is subject to review for site of service administration.** **Skyrizi (risankizumab-rzaa) IV may be considered medically necessary for the treatment of ulcerative colitis when:** • Skyrizi (risankizumab-rzaa) IV is being prescribed by or in consultation with a gastroenterologist **AND** • Skyrizi (risankizumab-rzaa) IV is used only for induction therapy (administered at Week 0, Week 4, and Week 8 for a total of 3 IV infusions)

Drug	Medical Necessity for Ulcerative Colitis
	Skyrizi (risankizumab-rzaa) SC on-body injector may be considered medically necessary for the treatment of ulcerative colitis when: • Individual has received induction therapy with Skyrizi (risankizumab-rzaa) IV **AND** • Skyrizi (risankizumab-rzaa) SC on-body injector is being prescribed by or in consultation with a gastroenterologist
• **Tremfya (guselkumab) SC** • **Tremfya (guselkumab) IV**	**Tremfya (guselkumab) IV may be considered medically necessary for the treatment of ulcerative colitis when:** • Tremfya (guselkumab) IV is being prescribed by or in consultation with a gastroenterologist **AND** • Tremfya (guselkumab) IV is used only for induction therapy (administered at Week 0, Week 4, and Week 8 for a total of 3 IV infusions) **Tremfya (guselkumab) SC may be considered medically necessary for the treatment of ulcerative colitis when:** • Individual has received induction therapy with Tremfya (guselkumab) IV **AND** • Tremfya (guselkumab) SC is being prescribed by or in consultation with a gastroenterologist
First-line Janus Kinase Inhibitors	
• **Rinvoq (upadacitinib) oral** • **Xeljanz (tofacitinib) oral, immediate-release** • **Xeljanz XR (tofacitinib) oral, extended-release**	**Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended-release) may be considered medically necessary for the treatment of adult individuals with ulcerative colitis when:** • Individual is aged 18 years and older **AND** • Has had a trial and treatment failure with one or more TNF blockers **AND**

Drug	Medical Necessity for Ulcerative Colitis
	• Medication is prescribed by or in consultation with a gastroenterologist
Second-line α-4 Integrin Inhibitor	

Entyvio (vedolizumab) SC	**Entyvio (vedolizumab) SC may be considered medically necessary for the treatment of adult individuals with ulcerative colitis when:**
	• Individual is aged 18 years and older
	AND
	• Entyvio (vedolizumab) SC is being prescribed by or in consultation with a gastroenterologist
	AND
	• The individual has had a trial and treatment failure with two of the following:
	  ○ A preferred adalimumab product: Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)
	  ○ Omvoh (mirikizumab-mrkz) SC
	  ○ Rinvoq (upadacitinib)
	  ○ Simponi (golimumab) SC
	  ○ Skyrizi (risankizumab-rzaa) SC
	  ○ Stelara (ustekinumab) SC
	  ○ Xeljanz (tofacitinib) or Xeljanz XR (tofacitinib extended-release)
	  ○ Zymfentra (infliximab-dyyb)
	AND
	• Has received induction therapy with Entyvio (vedolizumab) IV
	OR
	• Has already started on or is currently undergoing induction therapy with Entyvio (vedolizumab) IV

Second-line IL-23 Inhibitor	
• **Omvoh (mirikizumab-mrkz) IV** • **Omvoh (mirikizumab-mrkz) SC**	**Omvoh (mirikizumab-mrkz) IV may be considered medically necessary for the treatment of adult individuals with ulcerative colitis when:** • Individual is aged 18 years and older

Drug	Medical Necessity for Ulcerative Colitis

	AND
	• Has had a trial and treatment failure with one of the following:
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Cyltezo (adalimumab-adbm)
	  ○ Simlandi (adalimumab-ryvk)
	  ○ Adalimumab-adaz (Hyrimoz unbranded)
	  ○ Adalimumab-adbm (Cyltezo unbranded)
	  ○ Adalimumab-ryvk (Simlandi unbranded)
	  ○ Skyrizi (risankizumab-rzaa) SC
	  ○ Stelara (ustekinumab) SC
	  ○ Zymfentra (infliximab-dyyb)
	AND
	• Omvoh (mirikizumab-mrkz) IV is being prescribed by or in consultation with a gastroenterologist
	AND
	• Omvoh (mirikizumab-mrkz) IV is used only for induction therapy (administered at Week 0, Week 4, and Week 8 for a total of 3 IV infusions)
	
	Omvoh (mirikizumab-mrkz) SC may be considered medically necessary for the treatment of adult individuals with ulcerative colitis when:
	• Individual is aged 18 years and older
	AND
	• Has had a trial and treatment failure with one of the following:
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Cyltezo (adalimumab-adbm)
	  ○ Simlandi (adalimumab-ryvk)
	  ○ Adalimumab-adaz (Hyrimoz unbranded)
	  ○ Adalimumab-adbm (Cyltezo unbranded)
	  ○ Adalimumab-ryvk (Simlandi unbranded)
	  ○ Skyrizi (risankizumab-rzaa) SC
	  ○ Stelara (ustekinumab)
	  ○ Zymfentra (infliximab-dyyb)
	AND

Drug	Medical Necessity for Ulcerative Colitis
	• Has received induction therapy with Omvoh (mirikizumab-mrkz) IV **AND** • Omvoh (mirikizumab-mrkz) SC is being prescribed by or in consultation with a gastroenterologist
Second-line Sphingosine 1-Phosphate Receptor Modulators	

Velsipity (etrasimod) oral	**Velsipity (etrasimod) may be considered medically necessary for the treatment of adult individuals with ulcerative colitis when:**
	• Individual is aged 18 years and older
	AND
	• Has had a trial and treatment failure with TWO of the following:
	  ○ A preferred adalimumab product: Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)
	  ○ Omvoh (mirikizumab-mrkz) SC
	  ○ Rinvoq (upadacitinib)
	  ○ Simponi (golimumab) SC
	  ○ Skyrizi (risankizumab-rzaa) SC
	  ○ Stelara (ustekinumab) SC
	  ○ Xeljanz (tofacitinib) or Xeljanz XR (tofacitinib extended-release)
	  ○ Zymfentra (infliximab-dyyb)
	AND
	• Has had a trial and treatment failure with Zeposia (ozanimod)
	AND
	• Velsipity (etrasimod) is prescribed by or in consultation with a gastroenterologist
	AND
	• Dose is ≤ 2 mg per day

Zeposia (ozanimod) oral	**Zeposia (ozanimod) may be considered medically necessary for the treatment of adult individuals with ulcerative colitis when:** • Individual is aged 18 years and older **AND**

Drug	Medical Necessity for Ulcerative Colitis

	• Has had a trial and treatment failure with TWO of the following:
	  ○ A preferred adalimumab product: Humira (adalimumab) (AbbVie) [NDCs starting with 00074], Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)
	  ○ Skyrizi (risankizumab-rzaa) SC
	  ○ Stelara (ustekinumab) SC
	  ○ Zymfentra (infliximab-dyyb)
	AND
	• Zeposia (ozanimod) is prescribed by or in consultation with a gastroenterologist
	AND
	• Dose is ≤ 0.92 mg per day

Second-line TNF-α Inhibitors	

• **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) SC**
• **Idacio (adalimumab-aacf) SC**
• **Yuflyma (adalimumab-aaty) 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), Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty), and Yusimry (adalimumab-aqvh) may be considered medically necessary for the treatment of ulcerative colitis when:
	• Individual has had a trial and treatment failure with ALL the following:
	  ○ Cyltezo (adalimumab-adbm) OR adalimumab-adbm (Cyltezo unbranded)
	  ○ Humira (adalimumab) (AbbVie) [NDCs starting with 00074]
	  ○ Adalimumab-adaz (Hyrimoz unbranded)
	  ○ Simlandi (adalimumab-ryvk) OR adalimumab-ryvk (Simlandi unbranded)
	AND
	• Medication is being prescribed by or in consultation with a gastroenterologist

Drug	Medical Necessity for Ulcerative Colitis
• **Yusimry (adalimumab-aqvh) SC**	
Simponi (golimumab) SC	**Simponi (golimumab) may be considered medically necessary for the treatment of ulcerative colitis when:** • Individual has had a trial and treatment failure with Cyltezo (adalimumab-adbm) OR Humira (adalimumab) (AbbVie) [NDCs starting with 00074] OR Simlandi (adalimumab-ryvk) OR adalimumab-adaz (Hyrimoz unbranded) OR adalimumab-adbm (Cyltezo unbranded) OR adalimumab-ryvk (Simlandi unbranded) **AND** • Medication is being prescribed by or in consultation with a gastroenterologist
• **Avsola (infliximab-axxq) IV,** • **Renflexis (infliximab-abda) IV**	**Avsola (infliximab-axxq) and Renflexis (infliximab-abda) are subject to review for site of service administration.** **Avsola (infliximab-axxq) and Renflexis (infliximab-abda) may be considered medically necessary for the treatment of ulcerative colitis when:** • The individual has had an inadequate response or intolerance to Inflectra (infliximab-dyyb), Infliximab (Janssen – unbranded), or Remicade (infliximab) **AND** • The medication is prescribed by or in consultation with a gastroenterologist

Drug	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, policy 5.01.550, or policy 5.01.564 are considered investigational.**

Drug	Not Medically Necessary
As listed	**All other uses of the drugs for approved conditions listed in this policy are considered not medically necessary.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Stelara (ustekinumab) IV may be approved for 30-days to allow for a one-time induction dose. Omvoh (mirikizumab-mrkz) IV, Skyrizi (risankizumab-rzaa) IV, and Tremfya (guselkumab) IV may be approved for 90-days to allow for induction therapy. All other drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Future re-authorization of all drugs, excluding Stelara (ustekinumab) IV, Omvoh (mirikizumab-mrkz) IV, Skyrizi (risankizumab-rzaa) IV, and Tremfya (guselkumab) IV listed in policy may be approved up to 3 years 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
Reviewed for Medical Necessity	
HCPCS	
C9168	Injection, mirikizumab-mrkz (Omvoh), 1 mg (code termed effective 7/1/24)
C9399	Unclassified drugs or biologicals (used to report Omvoh)

Code	Description
J0135	Injection, adalimumab (Humira), 20 mg
J0717	Injection, certolizumab pegol (Cimzia), 1 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)
J1628	Injection, guselkumab (Tremfya), 1 mg
J1745	Injection, infliximab, excludes biosimilar (Remicade or Janssen unbranded), 10 mg
J2267	Injection, mirikizumab-mrkz, (Omvoh) 1 mg (new code effective 7/1/2024)
J2323	Injection, natalizumab, (Tysabri), 1 mg
J2327	Injection, risankizumab-rzaa, intravenous, (Skyrizi) 1 mg
J3357	Injection, ustekinumab (Stelara), 1 mg
J3358	Ustekinumab, for intravenous injection, (Stelara),1 mg
J3380	Injection, vedolizumab (Entyvio), 1 mg
J3590	Unclassified biologics (Use to report Amjevita, Simponi, Cyltezo, Hyrimoz HCF, Adalimumab-adaz HCF (Sandoz – unbranded), Abrilada, Hadlima, Hulio, Hyrimoz LCF, Omvoh, Simlandi, Yuflyma, Yusimry, and Zymfentra)
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg
Q5131	Injection, adalimumab-aacf, biosimilar, (IDACIO), 20 mg
Q5134	Injection, natalizumab-sztn (Tyruko), biosimilar, 1 mg (new code effective 4/1/2024)

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

Age Considerations

Age limits specified in this policy are determined according to 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.

Evidence Review

Crohn's Disease (CD)

The American College of Gastroenterology indicates current therapeutic recommendations depend on disease location, disease severity, and the presence of disease-associated complications. Pharmacologic approaches include various 5-aminosalicylates (5-ASAs), corticosteroids, and immunosuppressants. While the effectiveness of the 5-ASAs is less than corticosteroids, their side effect profile is more favorable. Azathioprine and sulfasalazine are also associated with clinically significant long-term toxicity, according to the National Cooperative Crohn's Disease Study. Azathioprine, sulfasalazine, and prednisone have not been demonstrated to prevent recurrence of disease flares.

Surgical resection is a common occurrence in CD, with up to 57% of individuals requiring at least one surgery in any given year. Within 10 years of disease onset, 71% of individuals undergo this therapy.

Clinical trials with Remicade (infliximab) in individuals with moderate to severe CD have shown that Remicade significantly reduces symptoms, improves quality of life, provides endoscopic evidence of mucosal healing, and reduces recurrence rates allowing for fewer hospitalizations and invasive procedures. Additionally, individuals with fistulizing disease were able to achieve a reduction in the number of draining enterocutaneous and rectovaginal fistulas.

Inflectra (infliximab-dyyb) is a biosimilar to Remicade (infliximab) approved for the same indications, with the exception of ulcerative colitis in pediatric individuals. For a full list of indications and details on the clinical trials information please refer to the package insert for Inflectra. The safety and efficacy of adalimumab (Humira) for the induction and/or maintenance

of remission in individuals with moderately to severely active CD (Crohn's Disease Activity Index [CDAI] ≥220 and ≤450) was evaluated in four randomized placebo-controlled studies. Two of these studies evaluated Humira for induction of remission (defined as a CDAI <150), one study in individuals who were TNF antagonist naïve (CLASSIC-I) and the other in individuals who had lost response or were intolerant to Remicade (GAIN). Two of these studies evaluated Humira for maintenance of remission, both studies in individuals who were TNF antagonist naïve (CLASSIC-II and CHARM).

In CLASSIC-I, 299 individuals with moderately to severely active CD, including individuals with draining fistulas, were randomized to two subcutaneous injections at Weeks 0 and 2 with Humira 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo. Enrollees were also able to maintain existing therapy with immunomodulatory agents, corticosteroids, and/or aminosalicylates. The primary efficacy endpoint was induction of remission (CDAI <150) at Week 4. The rate of remission was significantly higher in the 160 mg/80 mg group (36%, p=0.001), but not for the 40 mg/20 mg (18%, p=0.36) or 80 mg/40 mg (24%, p=0.06) groups compared with placebo (12%). Injection site reactions occurred more frequently in Humira-treated individuals; otherwise, adverse events occurred at similar frequencies in all four treatment groups.

In GAIN, 325 individuals with moderately to severely active CD who were intolerant of, who had lost response, or who had an inadequate response to Remicade were randomized to two subcutaneous injections at Weeks 0 and 2 with Humira 160 mg/80 mg or placebo. Primary efficacy endpoint was induction of remission (CDAI <150) at Week 4. Clinical response (decrease in CDAI score ≥70 or 100) at Week 4 was also assessed. More Humira-treated individuals (21%, p<0.001) achieved clinical remission compared to those treated with placebo (7%). More Humira-treated individuals (52%, p<0.01) achieved a clinical response-70 compared with the placebo group (34%).

A total of 276 individuals participating in CLASSIC-I enrolled in CLASSIC-II and received open-label Humira 40 mg subcutaneously at Weeks 0 (Week 4 of CLASSIC-I) and 2. Those individuals (n=55) in remission at both Week 0 and Week 4 were re-randomized to Humira 40 mg QOW, 40 mg QW, or placebo for 52 additional weeks. Individuals who were not in remission at both Weeks 0 and 4 were treated with open-label Humira 40 mg QOW. These individuals were allowed to have their dose increase to 40 mg QW for non-response or disease flare. The re-randomized individuals were also allowed to "escape" into this open-label arm with disease flare. The primary efficacy endpoint was maintenance of remission (CDAI <150) in randomized individuals through week 56. Of the 55 individuals randomized at Week 4, a greater proportion receiving Humira (79% of the Humira 40 mg QOW group and 83% of the 40 mg QW group, both p<0.05) were in remission compared to the placebo group (44%). Of 204 individuals

entering the open-label arm, 46% were in remission at Week 56. Humira was generally well-tolerated.

In CHARM, a total of 854 individuals with moderately to severely active CD were treated with open-label Humira 80 mg at Week 0 followed by 40 mg at Week 2 as induction therapy. At Week 4, individuals were stratified by clinical response (decrease of CDAI ≥70) and randomized to double-blind treatment with subcutaneous Humira 40 mg QOW, Humira 40 mg QW, or placebo weekly for 52 additional weeks. The proportion of randomized clinical responders achieving clinical remission at Weeks 26 and 56 were coprimary endpoints. At Week 4, 499/854 (58%) of individuals achieved a clinical response-70 and were randomized to Humira or placebo. The percentage of randomized responders in remission was significantly greater in the Humira 40 mg QOW and 40 mg QW groups compared to the placebo group at Week 26 (40%, 47%, and 17%, respectively; $p<0.001$) and at Week 56 (36%, 41%, and 12%, respectively; $p<0.001$). No significant differences in efficacy were observed between the two active treatment groups. Individuals who did not achieve clinical response after 12 weeks were unlikely to achieve response. The safety profile for Humira was consistent with previous experience with the drug. More individuals receiving placebo (13.4%) discontinued treatment for an adverse event than those receiving Humira (6.9% in the 40 mg QOW and 4.7% in the 40 mg QW group).

Two randomized controlled Phase III trials, PRECiSE 1 and PRECiSE 2, demonstrated the safety and efficacy of Cimzia 400 mg SC at Weeks 0, 2, 4 and then every four weeks versus placebo for up to 24 weeks. In the induction study, individuals who had C-reactive protein (CRP) levels >10 mg/L at baseline who were treated with certolizumab had higher response rates than placebo-treated individuals (37% versus 26%; $p=0.04$) at Week 6. In the overall population, response rates were significantly higher with certolizumab vs. placebo (23% versus 16%; $p=0.02$). There were no significant differences in remission rates at Week 6 or 26 between certolizumab and placebo. Overall, certolizumab was well tolerated. The other trial investigated the efficacy of maintenance therapy in individuals that had completed a standard induction course. In this study 64% of all initially enrolled individuals achieved a clinical response (decrease in CDAI ≥150) at 6-weeks. Certolizumab produced significantly better maintenance of clinical response than placebo through Week 26 (62% versus 34%, $p < 0.001$) in individuals with CRP ≥ 10 mg/L. Maintenance treatment with CIMZIA showed significantly better remission rates than placebo at Week 26 (48% versus 29%, $p < 0.001$) in the ITT population. The adverse event profiles observed in these studies was similar to that seen with other anti-TNF agents.

The ENCORE, ENACT-1 and ENACT-2 trials found that the use of Tysabri in adults with moderate to severe CD significantly increased the percent of individuals with a clinical response and those in clinical remission. In individuals shown to be responders after 12-weeks of induction therapy, response rates and remission rates were significantly greater with Tysabri.

The percentage of individuals with sustained remission after withdrawal of oral steroids was also significantly greater with Tysabri versus placebo at Weeks 36 and 60. For assessment of quality of life, individuals treated with Tysabri experienced statistically and clinically significant improvements in both general measures (SF-36) and disease specific measures (IBDQ) beginning at Week 24 and continuing through Week 60 compared with placebo. From Week 24 through 60, individuals treated with Tysabri had quality of life scores consistent with remission.

A 12-week trial in CD individuals found a significantly higher incidence of headache, nasopharyngitis, and hypersensitivity-like reactions at Week 12. Development of anti-natalizumab antibodies at any post-baseline visit through Week 12 was more common with natalizumab vs. placebo. Exacerbation of CD and discontinuations due to adverse events were more common with placebo than with Tysabri at Week 60. There was a higher incidence at Week 60 of influenza with natalizumab compared to placebo. Viral infections were more common with natalizumab compared to placebo. At Week 12, there was a higher incidence of hypersensitivity reactions during infusion with natalizumab versus placebo.

Tysabri was initially approved for the treatment of multiple sclerosis in November 2004. It was withdrawn from the market by the manufacturer in February 2005 after three individuals in clinical trials developed progressive multifocal leukoencephalopathy (PML). The FDA stopped clinical trials for the product in February 2005. Following no new cases of PML, the FDA allowed Tysabri to return to the market in June 2006 with the requirement of a risk minimization program to be in place to limit use. Individual registration and periodic follow-up is also required. In August 2008, two additional cases of PML were reported in European Tysabri individuals, bringing the total to five. Both individuals were taking the drug for multiple sclerosis. Both had received at least one year of therapy, and neither was receiving any other biologic immunomodulator concurrently. The implications for Crohn's individuals remain unclear.

The TOUCH program requires distribution of Tysabri only through centralized or specialty pharmacies that have registered and follow the strict requirements of individual assessment, monitoring, education, and follow-up. Tysabri is currently only approved for monotherapy as it is unclear if the risks of PML increase with concurrent use of other immunosuppressives. Notably, the use of concomitant immunosuppressives was associated with PML in three cases, of which two individuals were being treated for MS and one for CD.

The safety and efficacy of vedolizumab (Entyvio) were evaluated in 3 Phase III, double blinded, placebo controlled, multicenter, randomized clinical trials—two in Crohn's disease and one in ulcerative colitis. There were total of 3,326 individuals participated in these trials. There were high discontinuation rates across all arms of the trials (51% to 62%), most often for a lack of efficacy (59% to 69%). Discontinuation did not appear to be different between placebo and drug arms and intention-to-treat efficacy analysis was performed to generate the data.

GEMINI 2 trial shows efficacy of vedolizumab in individuals with Crohn's disease. The study populations had a mean duration of disease of 9 (SD: 7.8) years and 51% of individuals were on glucocorticoids with median prednisone dose of 20 mg. At week 6, 15% of individuals in the vedolizumab arm and 7% of the individuals in the placebo arm had a clinical response (p=0.02). In the maintenance trial, which included only those responded to the induction therapy, 39% of those assigned to VDZ Q8W were in clinical remission at week 52, compared with 22% assigned to placebo (p<0.001). Clinical remission is defined as CDAI score ≤150. Durable clinical remission was 21% in the VDZ Q8W group compared with 14% in the placebo group (p=NS). Glucocorticoid-free remission was 32% in the VDZ Q8W compared with 16% in the placebo group (p=0.02).

GEMINI 3 trial tested the efficacy of vedolizumab in individuals with Crohn's disease, but it was discontinued after the induction phase due to lack of efficacy. The study authors explained that the statistically non-significant effect of vedolizumab as induction therapy could be related to the baseline disease severity and heavily pretreated disease state in the study population. Only the abstract is available on GEMINI 3 trial.

During the trial, 56 of 1434 (4%) of individuals treated with vedolizumab had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 individuals were persistently positive for anti-vedolizumab antibody and 33 of 56 individuals developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects with persistently positive anti-vedolizumab antibody, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

In April 2013, Feuerstein, et al., reported results of a systematic review of treatment recommendations by international guidelines for Crohn's disease. Of the 89% of guidelines that graded evidence, only 23% of treatment recommendations were supported by level A evidence, and 28% by level B; thus, approximately half the recommendations were based on lower quality evidence or expert opinion. This reflects the difficulties encountered in treating this perplexing disease. Policy updated to include new labeled indication of golimumab to treat ulcerative colitis. A full review of this policy will be scheduled later in the year.

August 2013: As the most recent U.S. and European guidelines for the treatment of adults with Crohn's disease call into question the efficacy of 5-ASAs for induction or maintenance of remission for this condition, their use prior to approval of a TNF-α inhibitor is no longer a requirement in Crohn's disease. The efficacy of 5-ASAs for induction or maintenance of remission in ulcerative colitis remains established and use prior to approval of a TNF α inhibitor remains a requirement in this condition.

However, several new themes or trends have been identified and should be followed. These included a potential new therapeutic goal of "deep remission", defined as a Cohn disease activity index (CDAI) score <150 and complete mucosal healing on endoscopy. A Crohn's Disease Digestive Damage Score (Lémann score) has been developed to measure cumulative bowel damage in individuals with this condition. Similar to the Sharp score for assessing joint damage in rheumatoid arthritis (RA), the Lémann score may be used to assess the effect of various pharmacological therapies, function as a clinical trial endpoint, and allow better identification of high-risk individuals in regard to identification or progression of bowel damage. Also analogous to RA, there is momentum growing in Crohn's for use of disease modifying agents (e.g., TNF-α inhibitors) early in the disease course to avoid later complications and need for surgery, particularly in individuals with poor prognostic factors. Combination therapy with an immunosuppressive and a TNF-α inhibitor is also promising. However, robust supporting scientific evidence for these emerging trends is still lacking. New compounds currently in phase II and/or III development for use in IBD include ustekinumab (Stelara), Xeljanz (tofacitinib), and vedolizumab.

Stelara (ustekinumab)

Stelara (ustekinumab) is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In in vitro models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's Disease. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

Stelara (ustekinumab) was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult individuals with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy. Studies CD-1 and CD-2 In studies CD-1 and CD-2, 1409 individuals were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6

and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, individuals were randomized to receive a single intravenous administration of Stelara at either approximately 6 mg/kg, placebo, or 130 mg (a lower dose than recommended).

In Study CD-1, individuals had failed or were intolerant to prior treatment with a TNF blocker: 29% individuals had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these individuals, 48% failed or were intolerant to one TNF blocker and 52% had failed2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the individuals were receiving corticosteroids and 31% of the individuals were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the Stelara approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, individuals had failed or were intolerant to prior treatment with corticosteroids (81% of individuals), at least one immunomodulator (6-mercaptopurine, azathioprine, methotrexate; 68% of individuals), or both (49% of individuals). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the individuals were receiving corticosteroids and 35% of the individuals were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 286 in the STELARA and 290 in the placebo group. In these induction studies, a greater proportion of individuals treated with Stelara achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo. Clinical response and remission were significant as early as Week 3 in Stelara treated individuals and continued to improve through Week 8.

Study CD-3

The maintenance study (CD-3) evaluated 388 individuals who achieved clinical response (≥100-point reduction in CDAI score) at Week 8 of induction with Stelara in studies CD-1 or CD-2. Individuals were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA every 8 weeks or placebo for 44 weeks. At Week 44, 47% of individuals who received STELARA were corticosteroid-free and in clinical remission, compared to 30% of individuals in the placebo group. At Week 0 of Study CD-3, 34/56 (61%) Stelara treated individuals who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these individuals were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) individuals were in clinical remission at Week 0 while 16/61 (26%) of these individuals were in remission at Week 44. At Week 0 of Study CD-3, 46/72 (64%) Stelara treated individuals who had previously failed Immunomodulator therapy or corticosteroids (but not TNF blockers) were

in clinical remission and 45/72 (63%) of these individuals were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these individuals were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these individuals who were also naïve to TNF blockers, 34/52 (65%) of Stelara treated individuals were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm. Individuals who were not in clinical response 8 weeks after STELARA induction were not included in the primary efficacy analyses for Study CD-3; however, these individuals were eligible to receive a 90 mg subcutaneous injection of Stelara upon entry into Study CD-3. Of these individuals, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

Ulcerative Colitis (UC)

Remicade (infliximab)

The safety and efficacy of Remicade were assessed in two randomized, double-blind, placebo-controlled clinical studies in 728 individuals with moderately to severely active ulcerative colitis (UC) with an inadequate response to conventional oral therapies.[15] In both studies, individuals were randomized to receive either placebo, 5 mg/kg Remicade or 10 mg/kg Remicade at Weeks 0, 2, 6, 14 and 22.

Individuals in study 1 had failed to respond or were intolerant to oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA). Individuals in study 2 had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of individuals in studies 1 and 2 were receiving corticosteroids (61% and 51%, respectively), 6-MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More individuals in study 2 then 1 were taking solely aminosalicylates for UC (26% versus 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by 30% and 3 points, accompanied by a decrease in the rectal bleeding subscore of 1 or a rectal bleeding subscore of 0 or 1.

In both studies, greater percentages of individuals in both Remicade groups achieved a clinical response, a sustained clinical response (response at both Weeks 8 and 30), clinical remission and other assessed clinical outcomes than in the placebo group. Of individuals on corticosteroids at baseline, greater proportions of individuals in the Remicade treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the individuals in the placebo treatment groups (22% in Remicade treatment groups vs. 10% in placebo group in study 1; 23% in Remicade treatment groups vs. 3% in placebo group in study 2). Clinical outcomes were generally similar in the Remicade 5 mg/kg and 10 mg/kg dose groups.

Humira (adalimumab)

After positive reports in small open-label trials, the safety and efficacy of adalimumab (Humira) was assessed in a multicenter, double-blinded randomized controlled trial in individuals with moderate to severe ulcerative colitis who were anti-TNF naïve and on stable suppressive therapy with oral corticosteroids and/or immunomodulators. A total of 576 individuals were randomized to receive either placebo, high dose (HD), or low dose (LD) adalimumab. HD was 180/60/40/40mg and LD was 80/40/40/40mg of adalimumab at Weeks 0, 2, 4, 6, respectively. Clinical remission was defined as a Mayo score ≤ 2 with subscores no greater than 1. Secondary outcomes included absolute score decrease plus decrease in rectal bleeding subscore, proportion with mucosal healing, and proportion with mild disease (including physician global assessment [PGA], rectal bleeding, and stool frequency subscores). Because the European regulatory authorities wanted to include a LD of adalimumab, there were two parts to the study, a 1:1 with HD (n=186) and a 1:1:1 portion of the study (n=390); results were pulled from the latter.

Twice as many individuals reached clinical remission at Week 8 with HD (p=0.031) therapy, while LD individuals were not significantly different versus placebo. Of the secondary outcomes, subscores in rectal bleeding and PGA showed improvement with significance vs. placebo in the HD arm. Individuals with higher baseline CRP levels had less instances of remission, and higher placebo rates were seen in Canadian and Eastern European centers than those in the US. Discontinuation rates were similar in each arm, with UC being the most common reason. Injection site pain was minimal and infection incidence was similar across groups, and malignancy was only seen in the placebo arm.

Simponi (golimumab)

The safety and efficacy of golimumab (Simponi) were evaluated in two multi-center, randomized, double-blind, placebo-controlled clinical trials in individuals ≥ 18 years of age (Trials UC-1 and UC-2). Trial UC-1 was an induction trial conducted in individuals with moderately to severely active UC, defined as a Mayo score of 6 to 12 [the Mayo score ranges from 0 to 12 and has four subscales that are each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment]. At baseline, subjects also had an endoscopy subscore of 2 or 3 on a 3-point scale (an endoscopy score of 2 is defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 is defined by spontaneous bleeding, ulceration). Individuals were corticosteroid

dependent (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response to or had failed to tolerate at least one of the following therapies: oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine.

Trial UC-1 was divided into 2 parts. In Part 1 (dose finding), individuals were randomized to one of 4 treatment groups: 400 mg golimumab administered subcutaneously (SC) at Week 0 and 200 mg at Week 2 (400/200 mg), 200 mg golimumab SC at Week 0 and 100 mg at Week 2 (200/100 mg), 100 mg golimumab SC at Week 0 and 50 mg at Week 2 (100/50 mg), or placebo SC at Weeks 0 and 2. In Part 2 (dose confirming), 771 individuals were randomized to receive either 400 mg golimumab SC at Week 0 and 200 mg at Week 2, 200 mg golimumab SC at Week 0 and 100 mg at Week 2, or placebo SC at Weeks 0 and 2. Golimumab 100/50 mg SC was not evaluated in Part 2; its safety and effectiveness has not been established in UC. Concomitant stable doses of oral aminosalicylates (5-ASA), oral corticosteroids (less than 40 mg/day), azathioprine (AZA), 6-mercaptopurine (6-MP), and/or methotrexate (MTX) were permitted. Individuals who received previous TNF inhibitors were excluded. The primary endpoint was the percent of individuals in clinical response at Week 6, defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time).

Trial UC-2 was a randomized-withdrawal maintenance trial that evaluated 463 individuals who achieved clinical response with golimumab induction and tolerated golimumab treatment. Individuals were randomized to receive golimumab 50 mg, golimumab 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, azathioprine, 6-mercaptopurine, and/or methotrexate were permitted. Corticosteroids were to be tapered at the start of the maintenance trial. The primary endpoint was the percentage of individuals maintaining clinical response through Week 54.

In Trial UC-1, a greater proportion of individuals achieved clinical response, clinical remission and had improvement of endoscopic appearance of the mucosa at Week 6 in the golimumab 200/100 mg group compared with the placebo group. The golimumab 400/200 mg group did not demonstrate additional clinical benefit over the golimumab 200/100 mg group. Clinical remission was defined as a Mayo score ≤ 2 points, with no individual subscore > 1. Improvement of endoscopic appearance of the mucosa was defined as a Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

In Trial UC-2, a greater proportion of individuals maintained clinical response through Week 54 in the golimumab 100 mg group compared with the placebo group. In Trial UC-2, golimumab-

treated individuals in clinical response (which included the subset of individuals in clinical remission) in Trial UC-1, were again assessed for clinical remission at Week 30 and Week 54. A greater proportion of individuals achieved clinical remission at both Weeks 30 and 54 without demonstrating a loss of response at any time point through Week 54 in the golimumab 100 mg group compared with the placebo group.

Entyvio (vedolizumab)

The GEMINI 1 trial tested the efficacy of vedolizumab in individuals with ulcerative colitis. The study populations had a mean duration of disease of 6.9 (SD: 6.4) years and 53% of individuals were on glucocorticoids with median prednisone dose of 20 mg. At week 6, 47.1% of individuals in the vedolizumab arm and 25.5% of the individuals in the placebo arm had a clinical response ($p<0.001$). In the maintenance trial, which included only those responded to the induction therapy, 41.8% of those assigned to VDZ Q8W were in clinical remission at week 52, compared with 15.9% assigned to placebo ($p<0.001$). Clinical remission is defined as a complete Mayo score of ≤2 points and no individual subscore >1 point. Durable clinical remission was 20.5% in the VDZ Q8W group compared with 8.7% in the placebo group ($p=0.008$). Glucocorticoid-free remission was 31.4% in the VDZ Q8W compared with 13.9% in the placebo group ($p<0.001$).

Xeljanz (tofacitinib)

Xeljanz (tofacitinib) 10mg twice daily was studied in two eight-week induction trials, OCTAVE Induction 1 (n=598) and Induction 2 (n=541), in moderate-severe ulcerative colitis in individuals previously treated with TNF-α antagonists. The primary end point was remission at 8 weeks. Individuals achieving remission were randomized to continue on maintenance therapy with either 5 or 10 mg twice daily or placebo. The primary end point was remission at 52 weeks. In OCTAVE Induction 1, remission at 8 weeks occurred in 18.5% of the tofacitinib individuals versus 8.2% in the placebo group ($P = 0.007$); in OCTAVE Induction 2, remission occurred in 16.6% versus 3.6% ($P<0.001$). In the OCTAVE Sustain trial, 34.3% of the individuals in the 5-mg group and 40.6% in the 10-mg group versus 11.1% in the placebo group ($P<0.001$ for both comparisons with placebo). In OCTAVE Induction, rates of serious infection were higher with tofacitinib than placebo. In OCTAVE Sustain, the rate of serious infection was similar across the three treatment groups, and the rates of overall infection and herpes zoster infection were higher with tofacitinib than placebo. Across all three trials, nonmelanoma skin cancer occurred in five tofacitinib individuals and one placebo individual. Cardiovascular events occurred in five

tofacitinib and no placebo individuals. Tofacitinib was associated with increased lipid levels versus placebo.

Zeposia (ozanimod)

The efficacy and safety of ozanimod were evaluated in two multicenter, randomized, double-blind, placebo-controlled clinical studies [UC Study 1 (induction) and UC Study 2 (maintenance) (NCT02435992)] in adult individuals with moderately to severely active ulcerative colitis.

In UC Study 1, a total of 645 individuals were randomized 2:1 to either ozanimod 0.92 mg given orally once daily or placebo for 10 weeks, beginning with a dosage titration. The trial included adult individuals with moderately to severely active UC who had an inadequate response or were intolerant to any of the following: oral aminosalicylates, corticosteroids, immunomodulators (e.g., 6-mercaptopurine and azathioprine), or a biologic (e.g., TNF blocker and/or vedolizumab). Individuals were required to be on stable doses of oral aminosalicylates and/or corticosteroids (prednisone daily dose up to 20 mg equivalent or budesonide extended-release tablets) prior to enrollment. Seventy-one percent of individuals were receiving mesalamine, 13% sulfasalazine, and 33% oral corticosteroids. A total of 30% of individuals had previously failed or were intolerant to TNF blockers. Of these individuals, 63% received at least two biologics including TNF blockers. The primary endpoint was clinical remission at Week 10, defined using a 3-component Mayo score without the physician global assessment: rectal bleeding subscore = 0, stool frequency subscore = 0 or 1 (and a decrease of ≥ 1 point from the baseline stool frequency subscore), and endoscopy subscore = 0 or 1 (an endoscopy subscore of 0 defined as normal or inactive disease, and an endoscopy subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability). A significantly greater proportion of individuals treated with ozanimod achieved clinical remission, clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement compared to placebo at Week 10.

In UC Study 2, a total of 457 individuals who received ozanimod in either UC Study 1 or in an open-label arm and achieved clinical response at Week 10 were re-randomized 1:1 and were treated with either ozanimod 0.92 mg (n=230) or placebo (n=227) for 42 weeks (UC Study 2), for a total of 52 weeks of treatment. Individuals were permitted to be on stable doses of oral aminosalicylates. Corticosteroid tapering was required upon entering this study for individuals who were receiving corticosteroids during the induction period. Concomitant oral immunomodulators or biologic therapies were not permitted. At study entry, 35% of individuals were in clinical remission; 29% of individuals were on corticosteroids; and 31% of individuals had an inadequate response, loss of response, or intolerance to TNF blockers. The primary endpoint

was the proportion of individuals in clinical remission at Week 52. After Week 52, 37% of ozanimod treated individuals and 19% percent of placebo treatment individuals had clinical remission for a treatment difference of 19% ($p<0.0001$).

Rinvoq (upadacitinib)

In two identical induction trials (UC-1; NCT02819635 and UC-2; NCT03653026), individuals were randomized 2:1 to receive either Rinvoq 45 mg once daily or placebo for 8 weeks. A total of 988 individuals were analyzed across the two trials. These trials included adult individuals with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapy. Enrolled individuals were permitted to use stable doses of oral aminosalicylates, methotrexate, ulcerative colitis-related antibiotics, and/or oral corticosteroids (up to 30 mg/day prednisone or equivalent). At baseline, 38% of individuals were receiving corticosteroids, and 68% of individuals were receiving aminosalicylates. Concomitant biologic therapies, azathioprine, 6-mercaptopurine, intravenous or rectal corticosteroids were prohibited. A total of 51% of individuals had previously failed treatment with or were intolerant to at least one biologic therapy.

Disease severity was assessed on the modified Mayo score (mMS), a 3-component Mayo score (0-9) which consists of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally read endoscopy score (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration. Enrolled individuals had a mMS between 5 to 9 with an ES of 2 or 3; at baseline the median mMS was 7, with 61% of individuals having a baseline mMS of 5 to 7 and 39% having a mMS of 8 to 9.

At baseline, 39% and 37% of individuals received corticosteroids, 1% and 1% of individuals received methotrexate, and 68% and 69% of individuals received aminosalicylates in UC-1 and UC-2, respectively. Individual disease severity was moderate (mMS ≤7) in 61% and 60% of individuals and severe (mMS >7) in 39% and 40% of individuals in UC-1 and UC-2, respectively. The primary endpoint was clinical remission defined using the mMS at Week 8. In Study UC-1, for Rinvoq 26% of the total population was in clinical remission at Week 8 vs. only 5% in the placebo group. In individuals with prior biologic therapy the rates of clinical remission were 18% for the Rinvoq vs. <1% for placebo. In Study UC-2, for Rinvoq 33% of the total population was in clinical remission at Week 8 vs. only 4% in the placebo group. In individuals with prior biologic therapy the rates of clinical remission were 30% for the Rinvoq vs. 2% for placebo.

The safety and efficacy of Rinvoq in the treatment of Crohn's disease (CD) was evaluated in two induction trials, CD-1 and CD-2. In these trials, individuals were randomized 2:1 to receive Rinvoq 45 mg or placebo once daily for the duration of 12 weeks. The Efficacy analysis included a total of 857 individuals (419 participants in CD-1 and 438 participants in CD-2) with moderately to severely active Crohn's disease, as indicated by a baseline Crohn's Disease Activity Index (CDAI) score of at least 220 and centrally reviewed Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 6 (or 4 for isolated ileal disease, excluding the narrowing component).

The primary efficacy endpoints were the proportion of individuals achieving clinical remission by week 12, and the proportion of individuals achieving endoscopic response (SES-CD) by week 12. The secondary efficacy endpoints included clinical response, corticosteroid-free remission, and endoscopic remission.

In the CD-1 trial, at the end of week 12, the placebo group had a clinical remission rate of 18% compared to 36% in the treatment group, with a p-value less than 0.001. Similarly, the endoscopic response was 3% in the placebo group compared to 34% in the treatment group, with p-value less than 0.001. The treatment group showed statistically significant responses in clinical response, corticosteroid-free clinical remission in individuals on corticosteroids at baseline, and endoscopic remission.

In CD-2 trial, at the end of week 12, the clinical remission rate of 23% in placebo group compared to 46% in the treatment group, with p value less than 0.001. Similarly, statistically significant responses were observed in clinical response, corticosteroid-free clinical remission in individuals on corticosteroids at baseline, and endoscopic remission in the treatment group.

In both trials, individuals in the treatment group experienced a greater reduction in stool frequency and abdominal pain compared to the placebo group. Furthermore, individuals in the treatment group also experienced clinically meaningful improvement in fatigue at week 12 compared to baseline and compared to placebo-treated individuals.

After completing the 12-week induction trials, a subset of 343 individuals who responded to 12 weeks of Rinvoq 45 mg induction therapy continued the maintenance study. These participants were randomized assigned to receive either Rinvoq 15 mg or Rinvoq 30 mg once daily or placebo for 52 weeks. The individuals in the treatment group achieved the primary endpoint of clinical remission and endoscopic response with p value less than 0.001. Additionally, the treatment group demonstrated secondary efficacy outcome of corticosteroid-free clinical remission, maintenance of clinical remission, endoscopic remission, clinical and endoscopic remission).

Velsipity (etrasimod)

The efficacy of Velsipity was evaluated in two randomized, double-blind, placebo-controlled Phase 3 studies: ELEVATE UC 52 and ELEVATE UC 12. Both trials included adults with moderately to severely active UC and an inadequate response, loss of response, or intolerance to at least one of the following treatment options: oral 5-ASAs, corticosteroids, thiopurines, JAK inhibitors, or biologic therapies. Nearly two-thirds of the individuals in the trials were naïve to a biologic or JAK inhibitor therapy. In both the ELEVATE UC 52 and ELEVATE UC 12 trials, Velsipity treatment resulted in improvements in the primary endpoint of clinical remission. In addition, key secondary endpoints in both trials were achieved in individuals treated with Velsipity. The most frequently reported adverse events (Aes) (in ≥5% of individuals) included headache, elevated liver tests, and dizziness. In both studies, overall infections, serious infections, and opportunistic infections (i.e. tuberculosis and cytomegalovirus infection) were similar between the treatment groups. Across both trials, four individuals had herpes zoster events. These events were considered either mild or moderate, were localized, and did not lead to discontinuation from the study. Four events of bradycardia or sinus bradycardia were reported in individuals who received Velsipity in the ELEVATE UC 52 study and five events were reported in the ELEVATE UC 12 trial. Two of the events were symptomatic and led to study discontinuation. One of the three asymptomatic individuals who discontinued the trial had both bradycardia and asymptomatic AV block second-degree Mobitz type I on Day 1. One additional asymptomatic individual discontinued the trial due to AV block, first degree, on Day 1. No AV block second-degree Mobitz type II or higher events were reported in either trial.

Omvoh (mirikizumab-mrkz)

The approval of Omvoh was based on results from the LUCENT program, which included two randomized, double-blind, placebo-controlled, Phase 3 clinical trials consisting of a 12-week induction study (LUCENT-1) and a 40-week maintenance study (LUCENT-2). In the studies, 41% of individuals in LUCENT-1 had failed at least one biologic and 3% had failed a Janus kinase (JAK) inhibitor. At Week 12, 24% of individuals achieved clinical remission compared to 15% in the placebo group in the LUCENT-1 trial. Of the individuals in LUCENT-2 who were treated with Omvoh for 52 weeks, 51% achieved clinical remission compared to 27% in the placebo group and 50% of individuals achieved steroid-free clinical remission at 1 year compared to 27% in the placebo group.

Tremfya (guselkumab)

The approval to treat ulcerative colitis was based on results from the ongoing QUASAR trial (NCT04033445), which included a Phase 2b dose-ranging induction study, a confirmatory Phase 3 induction study, and a Phase 3 maintenance study. Eligible participants demonstrated inadequate response or intolerance to other therapies for UC, including corticosteroids, other biologic agents, and Janus kinase (JAK) inhibitors. In the maintenance study, 50% of participants who received Tremfya 200 mg SC every 4 weeks, and 45% of participants who received Tremfya 100 mg SC every 8 weeks achieved the primary endpoint of clinical remission at Week 44, compared with 19% of participants who received placebo. Additionally, 34% of participants who received Tremfya 200 mg SC and 35% of those who received Tremfya 100 mg SC achieved endoscopic remission at Week 44, compared with 15% who received placebo.

Toxicities of TNF-α Antagonists

There have been no prospective trials evaluating safety among the TNF-α inhibitors. The risk of malignancies and serious infections has been studied to some depth retrospectively with the three older agents (adalimumab, etanercept and infliximab). The FDA did a meta-analysis of the available data in 2006 and found that the malignancy rates of individuals on TNF-α inhibitors are no higher than what is to be expected in this individual population. Another study done in 2007 found a higher incidence of cutaneous cancers among the TNF-α inhibitor treated individuals, irrespective of the agent. The newer agents are limited in their data breadth to demonstrate safety with respect to malignancies, but so far they compare similarly to the older agents. Long-term safety evaluations are necessary to validate this finding.

With regards to serious infections and tuberculosis, there are higher rates of serious infections while on the TNF-α inhibitors, compared to MTX alone. However, the retrospective studies do not come to an agreement on the actual risk. Infliximab showed higher rates of any infection compared to etanercept and adalimumab, and also showed higher rates of serious infections with the 10mg/kg dosing regimen versus the 3mg/kg dosing regimen. The newer agents (certolizumab and golimumab) showed increased risk of serious infections, but this data is not comparable with the older agents. This class of agents also has been associated with hepatitis B reactivation, CHF exacerbations, and new onset or exacerbation of demyelinating disorders.

2018 Update

A literature search was conducted from March 1, 2017, to March 5, 2018. No new studies were found that would require changes to policy. The toxicities of TNF inhibitors section revised to exclude non-IBD disease states.

2019 Update

A literature search was conducted from March 1, 2018, to May 31, 2019. No new studies were found that would require changes to policy.

2021 Update

Reviewed prescribing information for all drugs. No new evidence was identified that would require changes to drugs listed in this policy. Updated initial authorization duration for Stelara (ustekinumab) IV to 30-days to match policy criteria.

2022 Update

Reviewed prescribing information for all drugs. Added Infliximab (Janssen – unbranded) to policy with identical coverage criteria as brand Remicade (infliximab) for the treatment of Crohn's disease and ulcerative colitis (UC). Infliximab (Janssen – unbranded) is not a biosimilar and is the same as the approved brand Remicade without the brand name. Added coverage criteria for Rinvoq (upadacitinib) for the treatment of UC in individuals with an inadequate response or intolerance to one or more TNF blockers.

2023 Update

Reviewed prescribing information for all drugs. No new evidence was identified that would require changes to drugs listed in this policy. Added coverage criteria for Rinvoq (upadacitinib) for the treatment of adult individuals with moderately to severely active Crohn's disease. Updated Zeposia criteria to have a trial and treatment failure with one of the following: Amjevita (adalimumab-atto) [NDCs starting with 55513] and Humira (adalimumab) AND Individual has had a trial and treatment failure with Stelara (ustekinumab). Removed reference to

first-line treatment and second-line treatment from within the coverage criteria for all drugs. 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 CD and UC 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 CD and UC as preferred products and with the identical coverage criteria as Amjevita (adalimumab-atto) [NDCs starting with 55513]. Updated preferred Humira biosimilars (Cyltezo LCF, Hyrimoz HCF, Adalimumab-adaz HCF (Sandoz-unbranded)) along with Humira and Amjevita (NDC starting with 55513) in the list of agents to be tried and failed prior to using nonpreferred agents, such as Zeposia. 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 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 unbranded) 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. Added coverage criteria for Velsipity (etrasimod) for the treatment of ulcerative colitis.

2024 Update

Reviewed prescribing information for all drugs. Added coverage criteria for Tyruko (natalizumab-sztn) for the treatment of adult individuals with moderately to severely active Crohn's disease. Removed Stelara (ustekinumab) subcutaneous (SC) injection site of service requirement. Added site of service review for Skyrizi (risankizumab-rzaa) intravenous (IV). Added coverage criteria for Entyvio (vedolizumab) SC and Omvoh (mirikizumab-mrkz) for the treatment of ulcerative colitis. Updated step therapy requirements for Velsipity (etrasimod). 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

coverage criteria for Entyvio (vedolizumab) SC to include treatment of Crohn's disease. Updated non-preferred adalimumab coverage criteria to require trial and treatment failure with all preferred adalimumab products. Added Zymfentra (infliximab-dyyb) as a preferred product. Added Tyruko (natalizumab-sztn) to site of service requirement. Updated Skyrizi (risankizumab-rzaa) IV/SC coverage criteria to include treatment of certain individuals with ulcerative colitis. The following changes are effective January 3, 2025. Changed Avsola (infliximab-axxq) to a second-line agent. Updated coverage criteria for Avsola and Renflexis to require the individual to have an adequate trial and failure with Inflectra, Infliximab (Janssen – unbranded), or Remicade. Updated Hyrimoz (Sandoz) (adalimumab-adaz) [NDCs starting with 61314] from a preferred product to a non-preferred product. Updated Humira (AbbVie) (adalimumab) [NDCs starting with 00074] to require that the individual has had an inadequate response or intolerance to a preferred product for new starts. Added coverage criteria for Tremfya (guselkumab) IV/SC for the treatment of ulcerative colitis.

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History

Date	Comments
07/01/16	New policy, approved June 14, 2016. Add to Prescription Drug section. Policy content removed from 5.01.550. This policy addresses the medically necessary pharmacological treatment for IBD and includes site of service IV therapy administration criteria for applicable drugs.
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. Inclusion of Stelara with its new indication for use in Crohn's disease (along with the description and clinical trials information).

Date	Comments
12/01/16	Interim review, approved November 8, 2016. Clarification added regarding Inflectra's covered indications: not approved for pediatric UC.
03/14/17	Annual review, changes to become effective April 1, 2017. Added administration route to each drug, as well as included a statement on the status of IV agents being processed exclusively through the medical benefit.
03/22/17	Interim update. Cimzia in the setting of Crohn's disease now has an extra step that requires a trial and failure of either Humira or Stelara. Effective April 1, 2017.
04/10/17	Interim update. Policy section updated with infliximab (Remicade) IV and vedolizumab (Entyvio) moving to first-line agents, considered medically necessary as when criteria are met.
05/05/17	Minor update; added hyperlinks and step therapy graphs.
07/01/17	Interim review, approved June 13, 2017. Added coverage criteria for Renflexis (infliximab-abda). Added adalimumab step to Stelara SC.
07/14/17	Coding updated, added HCPCS code Q9989 (new code effective 7/1/17).
09/01/17	Interim review, approved August 15, 2017, Added coverage criteria for Xeljanz (tofacitinib) in Ulcerative Colitis. Clarified second line status of Stelara in Crohn's. Added Renflexis coding.
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 patient'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.
01/01/18	Coding update; added HCPCS code J3358 (new code effective 1/1/18).
02/14/18	Interim Review, approved February 6, 2018. Stelara has been moved from second line agent to first line agent for Crohn's Disease with removal of mandatory step through Humira in criteria. Approved February 13, 2018, to 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.
05/01/18	Annual Review, approved April 18, 2018. A literature search was conducted from 3/1/2017 to 3/5/2018. No new studies were found that would require changes to policy. Toxicities of TNF inhibitors section revised to exclude non-IBD disease states. Added suppositories as one of the options for corticosteroid and mesalamine products for ulcerative colitis. Dosing table was removed.
06/01/18	Interim Review approved May 17, 2018. Removed ulcerative colitis indication for Xeljanz as it is not FDA approved indication.
08/01/18	Interim Review, approved July 13, 2018. Added criteria and references for tofacitinib to treat ulcerative colitis.

Date	Comments
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Interim Review, approved December 13, 2018. Clarified criteria for Humira under the ulcerative colitis section.
02/01/19	Interim Review, approved January 8, 2019. Added tofacitinib to first-line treatment for ulcerative colitis.
03/01/19	Coding update: removed HCPCS code Q5102. Also added link to future version of policy that becomes effective June 9, 2019.
06/21/19	Revised the effective date of the updated policy from July 1, 2019, to July 31, 2019.
07/01/19	Annual Review, approved June 20, 2019. No changes to policy coverage criteria.
07/18/19	Removed link and note regarding updated policy.
09/01/19	Interim Review, approved August 22, 2019. Updated criteria for Cimzia.
11/01/19	Interim Review, approved October 8, 2019. Updated criteria for Xeljanz and Simponi SC when used for ulcerative colitis.
12/01/19	Interim Review, approved November 21, 2019. Added coverage criteria for Stelara IV and Stelara SC for the treatment of ulcerative colitis.
02/01/20	Interim Review, approved January 23, 2020. Added Xeljanz XR for UC with Xeljanz. Added Avsola (infliximab-axxq) to same status as Inflectra and Renflexis and removed note for non-indication for pediatric UC, now have indication per PI for all 3 agents. Added investigational table next to not medically necessary table for clarity and changed not medically necessary language. Added HCPCS code J3590 to report Avsola only.
07/01/20	Interim Review, approved June 18, 2020. Added Avsola as drug subject to site of service review. Changes to Avsola for site of service review are effective for dates of service on or after October 2, 2020, following 90-day provider notification. Effective July 1, 2020: Updated the Investigational table to include quantities that exceed the FDA labeled dosing for condition. Updated Stelara criteria for IV dosage form to a one-time induction dose. Removed J3590 and added Q5121 for Avsola.
10/01/20	Annual Review, approved September 8, 2020, effective January 1, 2021. Updated coverage criteria for Tysabri (natalizumab) adding trial and treatment failure with one prior agent. Added site of service review for Tysabri (natalizumab) for dates of service on or after January 1, 2021.
01/01/21	Interim Review, approved December 8, 2020. Updated Stelara (ustekinumab) coverage criteria from second-line to first-line therapy for the treatment of ulcerative colitis. For Crohn's disease medications updated the coverage criteria for Avsola, Cimzia, Entyvio, Humira, Inflectra, Remicade, Renflexis, Stelara, and Tysabri to require adequate trial and treatment failure with one corticosteroid or one other agent for Crohn's disease. For ulcerative colitis medications updated the coverage criteria for Avsola, Entyvio,

Date	Comments
	Humira, Inflectra, Remicade, Renflexis, Simponi, and Stelara to require adequate trial and treatment failure with one systemic agent. Added HCPCS code J3590 for Simponi.
05/01/21	Annual Review, approved April 22, 2021. Updated initial authorization duration for Stelara (ustekinumab) IV to 30-days.
08/01/21	Interim Review, approved July 13, 2021. Added coverage criteria for Zeposia (ozanimod) for the treatment of ulcerative colitis.
11/01/21	Interim Review, approved October 21, 2021. Added site of service review for Stelara (ustekinumab) IV and Stelara (ustekinumab) SC for dates of service on or after February 4, 2022.
01/01/22	Interim Review, approved December 21, 2021. Changed the re-authorization duration from 1-year to 3 years.
06/01/22	Annual Review, approved May 10, 2022. Removed reference to first-line treatment and second-line treatment from within the coverage criteria for all drugs. Added Infliximab (Janssen – unbranded) to policy with identical site-of-service requirements and coverage criteria as brand Remicade (infliximab) for the treatment of CD and UC. Moved Inflectra (infliximab-dyyb) to a first-line TNF-α antagonists for the treatment of CD and UC. Updated coverage criteria for Renflexis (infliximab-abda) and Avsola (infliximab-axxq) for the treatment of CD and UC to require the patient has had an inadequate response or intolerance to Infliximab (Janssen – unbranded), Inflectra (infliximab-dyyb), or Remicade (infliximab). Updated Zeposia (ozanimod) criteria to require dose is ≤ 0.92 mg per day. Updated Xeljanz and Xeljanz XR for the treatment of UC to require a trial and treatment failure with one or more TNF blockers. Added coverage criteria for Rinvoq for the treatment of UC.
09/01/22	Interim Review, approved August 9, 2022. Updated coverage criteria for Cimzia Stelara IV, Stelara SC, and Tysabri to include coverage for patients with enterocutaneous or rectovaginal fistulas and for patients that have had ileocolonic resection. Added coverage criteria for Skyrizi (risankizumab-rzaa) IV and Skyrizi (risankizumab-rzaa) SC on-body injector for the treatment of moderately to severely active Crohn's disease. Added mesalamine to the list of systemic agent example drugs for the treatment of UC. Updated Tysabri criteria to include requirement the patient has had a trial and treatment failure with one or more TNF blockers. Changes to Tysabri for the TNF requirement are effective for dates of service on or after December 1, 2022, following 90-day provider notification.
01/01/23	Coding update. Removed Skyrizi from HCPC code J3590 and added new HCPC code J2327.
02/01/23	Interim Review, approved January 10, 2023. Added coverage for the biosimilar Amjevita (adalimumab-atto) for the treatment of CD and UC with the identical coverage criteria as Humira (adalimumab). Added Amjevita as a prerequisite medication, on par with Humira, to all the medications in policy that include Humira as a prerequisite medication. Changed Zeposia (ozanimod) criteria for the treatment of UC from try and fail two prerequisite medications to one prerequisite medication.

Date	Comments
	Changed the wording from "patient" to "individual" throughout the policy for standardization. Added Amjevita to HCPC code J3590.
03/01/23	Interim Review, approved February 14, 2023. For all CD drugs added coverage for individuals currently taking a corticosteroid medication. For all CD drugs added methylprednisolone and mesalamine extended-release (Pentasa formulation) as example medications. Updated UC criteria for Amjevita, Avsola, Entyvio, Humira, Inflectra, Infliximab (Janssen – unbranded), Remicade, Renflexis, Simponi SC, Stelara IV, Stelara SC, and Zeposia removing the requirement the individual has tried and failed one traditional systemic agent or has pouchitis.
04/01/23	Annual Review, approved March 14, 2023. Added clarification of coverage for the biosimilar Amjevita (adalimumab-atto) with NDCs starting with 55513 versus NDCs starting with 72511. Changed the wording from "patient" to "individual" throughout the policy for standardization.
07/01/23	Interim Review, approved June 13, 2023. Added new HCPCS code Q5131. Added coverage criteria for Rinvoq (upadacitinib) for the treatment of adult individuals with moderately to severely active Crohn's disease. Updated Zeposia criteria to have a trial and treatment failure with one of the following: Amjevita (adalimumab-atto) [NDCs starting with 55513] and Humira (adalimumab) AND Individual has had a trial and treatment failure with Stelara (ustekinumab). Removed reference to first-line treatment and second-line treatment from within the coverage criteria for all drugs.
08/01/23	Interim Review, approved July 11, 2023. 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 CD and UC 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 CD and UC 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.
08/01/23	Interim Review, approved July 24, 2023. Updated preferred Humira biosimilars (Cyltezo LCF, Hyrimoz HCF, Adalimumab-adaz HCF (Sandoz-unbranded)) along with Humira and Amjevita (NDC starting with 55513) in the list of agents to be tried and failed prior to using nonpreferred agents, such as Zeposia.
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 a 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-

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	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.
01/01/24	Interim Review, approved December 12, 2023. 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 unbranded) 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 coverage criteria for Velsipity (etrasimod) for the treatment of ulcerative colitis.
02/01/24	Annual Review, approved January 9, 2024. Added coverage criteria for Tyruko (natalizumab-sztn) for the treatment of adult individuals with moderately to severely active Crohn's disease. Added Tyruko to HCPC code J3590.
03/01/24	Interim Review, approved February 13, 2024. Removed Stelara (ustekinumab) subcutaneous (SC) injection site of service requirement. Added coverage criteria for Entyvio (vedolizumab) SC and Omvoh (mirikizumab-mrkz) for the treatment of ulcerative colitis. Updated step therapy requirements for Velsipity (etrasimod). The following policy changes are effective on or after June 7, 2024, following 90-day provider notification: added site of service review for Skyrizi (risankizumab-rzaa) intravenous (IV). Added HCPCS code C9399 for Omvoh.
04/01/24	Coding update. Added new HCPCS code C9168.
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 coverage criteria for Entyvio (vedolizumab) SC to include treatment of Crohn's disease. Updated non-preferred adalimumab coverage criteria to require trial and treatment failure with all preferred adalimumab products. Added Simlandi to J3590. Added HCPCS code J2267 and terminated HCPCS code C9168, effective 7/1/2024.
08/01/24	Interim Review, approved July 22, 2024. Added Zymfentra (infliximab-dyyb) as a preferred product. Added Zymfentra to J3590.
09/01/24	Interim Review, approved August 13, 2024. Updated Skyrizi (risankizumab-rzaa) IV/SC coverage criteria to include treatment of certain individuals with ulcerative colitis. The following policy changes are effective December 5, 2024, following 90-day provider notification. Added Tyruko (natalizumab-sztn) to site of service requirement. Added HCPCS code Q5134 for Tyruko.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Changed Inflectra (infliximab-dyyb) to a first-line agent. Changed Avsola (infliximab-axxq) to a second-line agent. Updated coverage criteria for Avsola and Renflexis to require the individual to have an adequate trial and failure with Inflectra, Infliximab (Janssen – unbranded), or

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	Remicade. Updated Hyrimoz (Sandoz) (adalimumab-adaz) [NDCs starting with 61314] from a preferred product to a non-preferred product. Updated Humira (AbbVie) (adalimumab) [NDCs starting with 00074] to require that the individual has had an inadequate response or intolerance to a preferred product for new starts. Added J1628 for Tremfya.
11/01/24	Interim Review, approved October 8, 2024. Added coverage criteria for Tremfya (guselkumab) IV/SC for the treatment of ulcerative colitis. Added HCPCS code J1628 for Tremfya.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.