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Ustekinumab and Associated Biosimilars

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Stelara®, Imuldosa, Otulfi, Pyzchiva®, Selarsdi, Steqeyma, Wezlana™, and Yesintek™ may be self-administered. For self-administered medications, please refer to applicable pharmacy benefit plan.

A single intravenous administration of ustekinumab (Stelara®) or ustekinumab-srlf (Imuldosa), or ustekinumab-aauz (Otulfi), or ustekinumab-ttwe (Pyzchiva®), or ustekinumab-aekn (Selarsdi), or ustekinumab-stba (Steqeyma), or ustekinumab-auub (Wezlana™) or ustekinumab-kfce (Yesintek™) **may be considered medically necessary** for the treatment of:

- Adults 18 years and older with either:
  - Moderately to severely active Crohn's disease (CD); or
  - Moderately to severely active ulcerative colitis (UC).

NOTE 2: When meeting criteria noted above, adults with Crohn's disease or ulcerative colitis will receive the first dose through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. Patients may then receive as an injection under the skin (subcutaneous injection) 8 weeks after the first dose.

Intravenous administration of ustekinumab (Stelara®) and its biosimilars **is considered experimental, investigational, and/or unproven** for all other indications.

NOTE 3: Ustekinumab (Stelara®) and its biosimilars shall not be used concurrently with other biologics used to treat the indications above. Please refer to the Description Section for a list of biological disease-modifying antirheumatic drugs (DMARDs).

Policy Guidelines

None.

Description

The following table contains a list of some, but not all, biologic DMARDs applicable to this policy, and is not all-inclusive.

Table 1. Biological disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
abatacept	Orencia

adalimumab	Humira
anakinra	Kineret
apremilast	Otezla
baricitinib	Olumiant
brodalumab	Siliq
certolizumab pegol	Cimzia
etanercept	Enbrel
golimumab	Simponi/Simponi Aria
guselkumab	Tremfya
infliximab	Remicade/Avsola/Inflectra/Infliximab (unbranded)/Renflexis
ixekizumab	Taltz
risankizumab-rzaa	Skyrizi
rituximab	Rituxan/Riabni/Ruxience/Truxima
sarilumab	Kevzara
secukinumab	Cosentyx
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
tofacitinib	Xeljanz
upadactinib	Rinvoq
vedolizumab	Entyvio

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology. Ustekinumab may be administered by both intravenous infusion and by subcutaneous injection.

Ustekinumab reduces the immune system's ability to fight infections. Infections can be caused by viruses, fungi, or bacteria that have spread throughout the body. There may also be an increased risk of developing cancer. In addition, patients being treated with ustekinumab should not receive live vaccines. Bacille Calmette-Guerin (BCG) vaccines should not be given during treatment with Stelara or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to patient.

Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal (GI) tract. It belongs to a group of conditions known as inflammatory bowel diseases (IBD). While the disease can occur at any age, it is most often diagnosed in adolescents and adults between the ages of 20 and 30. While more common in Caucasians, Crohn's can affect people from all ethnic backgrounds. Rates are increasing among Hispanics and Asians. Crohn's may affect any part of the GI tract, but most commonly the end of the small bowel (ileum) and the beginning of the colon are affected. It can also affect the entire thickness of the bowel wall; and the inflammation may leave normal areas in between patches of diseased intestine. (2)

Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory disease of the large intestine (colon) that affects the lining of the colon and causes small sores or ulcers to form. Those ulcers then can produce pus and mucous, which cause abdominal pain and frequent bowel movements. Most people are diagnosed in their mid-30s; but older men are more likely to be diagnosed than older women. The risk of developing UC is between 1.6% and 30% if you have a first-degree relative with the disease. UC can affect anyone regardless of racial or ethnic group. (2)

Regulatory

The U.S. Food and Drug Administration (FDA) approvals for Stelara and its biosimilars are provided in Table 2.

Table 2. U.S. Food and Drug Administration Approval

Drug/Biosimilar	Year Approved	Indication(s)
Stelara (ustekinumab) (3)	2016 2019	Adults with moderately to severely active CD Adults with moderately to severely active UC
Wezlana (ustekinumab-auub) (5)	2023	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Imuldosa (ustekinumab-srlf) (6)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Otulfi (ustekinumab-aauz) (7)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Pyzchiva® (ustekinumab-ttwe) (8)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Selarsdi (ustekinumab-aekn) (9)	2024	Adults with moderately to severely active CD and for the treatment of adults with

		moderately to severely active UC
Steqeyma (usteminumab-stba (11)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Yesintek™ (ustekinumab-kfce) (10)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC

CD: Crohn's disease; UC: ulcerative colitis.

Rationale

This policy was originally developed in 2020 and is based on the U.S. Food and Drug Administration (FDA) labeled indications through February 2024.

Crohn's Disease (CD) (1, 4, 6-11)
Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients 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. Patients in CD-1 had failed or were intolerant to treatment with one or more TNF blockers, while patients in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Studies CD-1 and CD-2
In studies CD-1 and CD-2, 1409 patients 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, patients were randomized to receive a single intravenous administration of ustekinumab at approximately 6 mg/kg, placebo, or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients 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 patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the

patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 319 in the ustekinumab approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-MP, AZA, MTX; 68% of patients), or both (49% of patients). 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 patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 286 in the ustekinumab and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with ustekinumab (at the recommended dose of approximately 6 mg/kg dose) achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 3 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in ustekinumab-treated patients and continued to improve through Week 8.

Table 3. Induction of Clinical Response and Remission in CD-1* and CD-2**

	CD-1 n = 741			**CD-2 n = 627**		
	Placebo N = 247	**ustekinumab[a] N = 249**	**Treatment difference and 95% CI**	**Placebo N = 209**	**ustekinumab[a] N = 209**	**Treatment difference and 95% CI**
Clinical response (100 point), week 6	53 (21%)	84 (34%)[b]	12% (4%, 20%)	60 (29%)	116 (56%)[c]	27% (18%, 36%)
Clinical remission week 8	18 (7%)	52 (21%)[c]	14% (8%, 20%)	41 (20%)	84 (40%)[c]	21% (12%, 29%)
Clinical response (100 point), week 8	50 (20%)	94 (38%)[c]	18% (10%, 25%)	67 (32%)	121 (58%)[c]	26% (17%, 35%)
70 Point response, week 6	75 (30%)	109 (44%)[b]	13% (5%, 22%)	81 (39%)	135 (65%)[c]	26% (17%, 35%)
70 Point response, week 3	67 (27%)	101 (41%)[b]	13% (5%, 22%)	66 (32%)	106 (51%)[c]	19% (10%, 28%)

CI: confidence interval.

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70-point response is defined as reduction in CDAI score by at least 70 points.
* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy.
** Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-MP, AZA, MTX) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.
[a] Infusion dose of ustekinumab using a weight-based dosage regimen.
[b] $0.001 \leq p < 0.01$.
[c] $p < 0.001$.

Study CD-3

The maintenance study (CD-3) evaluated 388 patients who achieved clinical response (≥100-point reduction in CDAI score) at Week 8 with either induction dose of ustekinumab in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks or placebo for 44 weeks (see Table 4).

Table 4. Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N=131[a]	**90mg ustekinumab every 8 weeks N=128[a]**	**Treatment difference and 95% CI**
Clinical Remission	47 (36%)	68 (53%)[b]	17 (5%, 29%)
Clinical Response	58 (44%)	76 (59%)[c]	15% (3%, 27%)
Clinical Remission in patients in remission at the start of maintenance therapy**	36/79 (46%)	52/78 (67%)[b]	21% (6%, 36%)

CI: confidence interval.
Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission.
* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
** Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.
[a] Patients who achieved clinical response to ustekinumab at the end of the induction study.
[b] $p < 0.01$
[c] $0.01 \leq p < 0.05$

At Week 44, 47% of patients who received ustekinumab were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) ustekinumab treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these

patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) ustekinumab treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of ustekinumab treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after ustekinumab induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of ustekinumab upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

Ulcerative Colitis (UC) (1, 4, 6-11)

Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical studies [UC-1 and UC-2 (NCT02407236)] in adult patients with moderately to severely active UC who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or 6-MP or AZA therapy. The 8-week intravenous induction study (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance study (UC-2) for a total of 52 weeks of therapy.

Disease assessment was based on the Mayo score, which ranged from 0 to 12 and has four subscores that were each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally-reviewed endoscopy, and physician global assessment. Moderately to severely active UC was defined at baseline (Week 0) as Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥2. An endoscopy score of 2 was defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous bleeding, ulceration. At baseline, patients had a median Mayo score of 9, with 84% of patients having moderate disease (Mayo score 6-10) and 15% having severe disease (Mayo score 11-12).

Patients in these studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents (AZA, 6-MP, or MTX), and oral corticosteroids (prednisone).

<u>Study UC-1</u>

In UC-1, 961 patients were randomized at Week 0 to a single intravenous administration of ustekinumab of approximately 6 mg/kg, 130 mg (a lower dose than recommended), or placebo. Patients enrolled in UC-1 had to have failed therapy with corticosteroids, immunomodulators or at least one biologic. A total of 51% had failed at least one biologic and 17% had failed both a

TNF blocker and an integrin receptor blocker. Of the total population, 46% had failed corticosteroids or immunomodulators but were biologic-naïve and an additional 3% had previously received but had not failed a biologic. At induction baseline and throughout the study, approximately 52% patients were receiving oral corticosteroids, 28% patients were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% patients were receiving aminosalicylates.

The primary endpoint was clinical remission at Week 8. Clinical remission with a definition of: Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0 (no rectal bleeding), and Mayo endoscopy subscore of 0 or 1 (Mayo endoscopy subscore of 0 defined as normal or inactive disease and Mayo subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability) is provided in Table 5.

The secondary endpoints were clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement. Clinical response with a definition of (≥ 2 points and ≥ 30% decrease in modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1), endoscopic improvement with a definition of Mayo endoscopy subscore of 0 or 1, and histologic-endoscopic mucosal improvement with a definition of combined endoscopic improvement and histologic improvement of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) provided in Table 5.

In UC-1, a significantly greater proportion of patients treated with ustekinumab (at the recommended dose of approximately 6 mg/kg dose) were in clinical remission and response and achieved endoscopic improvement and histologic-endoscopic mucosal improvement compared to placebo (see Table 5).

Table 5. Proportion of Patients Meeting Efficacy Endpoints in Week 8 in UC-1

Endpoint	**Placebo N = 319**		**Ustekinumab[a] N = 322**		**Treatment Difference and 97.5% CI[g]**
	N	**%**	**N**	**%**	
Clinical Remission[c]	**22**	**7%**	**62**	**19%**	12% (7%, 18%)[h]
Bio-naïve[b]	14/151	9%	36/147	24%	
Prior biologic failure	7/161	4%	24/166	14%	
Endoscopic Improvement[d]	**40**	**13%**	**80**	**25%**	12% (6%, 19%)[h]
Bio-naïve[b]	28/151	19%	43/147	29%	
Prior biologic failure	11/161	7%	34/166	20%	

Clinical Response[e]	**99**	**31%**	**186**	**58%**	27% (18%, 35%)[h]
Bio-naïve[b]	55/151	36%	94/147	64%	
Prior biologic failure	42/161	26%	86/166	52%	
Histologic-Endoscopic Mucosal Improvement[f]	**26**	**8%**	**54**	**17%**	9% (3%, 14%)[h]
Bio-naïve[b]	19/151	13%	30/147	20%	
Prior biologic failure	6/161	4%	21/166	13%	

UC: ulcerative colitis
CI: confidence interval
[a] Infusion dose of ustekinumab using a weight-based dosage regimen.
[b] An additional 7 patients on placebo and 9 patients on ustekinumab (6 mg/kg) had been exposed to, but had not failed, biologics.
[c] Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).
[d] Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).
[e] Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
[f] Histologic-endoscopic mucosal improvement was defined as combined endoscopic improvement (Mayo endoscopy subscore of 0 or 1) and histologic improvement of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).
[g] Adjusted treatment difference (97.5% CI)
[h] $p < 0.001$

The relationship of histologic-endoscopic mucosal improvement, as defined in UC-1, at Week 8 to disease progression and long-term outcomes was not evaluated during UC-1.

Rectal Bleeding and Stool Frequency Subscores
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in ustekinumab treated patients.

Study UC-2
The maintenance study (UC-2) evaluated 523 patients who achieved clinical response 8 weeks following the intravenous administration of either induction dose of ustekinumab in UC-1. These patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, or every 12 weeks (a lower dose than recommended), or placebo for 44 weeks.

The primary endpoint was the proportion of patients in clinical remission at Week 44. The secondary endpoints included the proportion of patients maintaining clinical response at Week 44, the proportion of patients with endoscopic improvement at Week 44, the proportion of patients with corticosteroid-free clinical remission at Week 44, and the proportion of patients

maintaining clinical remission at Week 44 among patients who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in patients treated with ustekinumab at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 6.

Table 6. Efficacy Endpoints of Maintenance at Week 44 in UC-2 (52 Weeks from Initiation of the Induction Dose)

Endpoint	**Placebo[b] N = 175**		**90mg Ustekinumab Every 8 Weeks N = 176**		**Treatment Difference and 95% CI**
	N	**%**	**N**	**%**	
Clinical Remission[c]	**46**	**26%**	**79**	**45%**	19% (9%, 28%)[g]
Bio-naïve[a]	30/84	36%	39/79	49%	
Prior biologic failure	16/88	18%	37/91	41%	
Maintenance of Clinical Response at Week 44[d]	**84**	**48%**	**130**	**74%**	26% (16%, 36%)[g]
Bio-naïve[a]	49/84	58%	62/79	78%	
Prior biologic failure	35/88	40%	64/91	70%	
Endoscopic Improvement[e]	**47**	**27%**	**83**	**47%**	20% (11%, 30%)[g]
Bio-naïve[a]	29/84	35%	42/79	53%	
Prior biologic failure	18/88	20%	38/91	42%	
Corticosteroid-free Clinical Remission[f]	**45**	**26%**	**76**	**43%**	17% (8%, 27%)[g]
Bio-naïve[a]	30/84	36%	38/79	48%	
Prior biologic failure	15/88	17%	35/91	38%	
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 8 weeks after induction	**18/50**	**36%**	**27/41**	**66%**	31% (12%, 50%)[h]
Bio-naïve[a]	12/27	44%	14/20	70%	
Prior biologic failure	6/23	26%	12/18	67%	

CI: confidence interval.

[a] An additional 3 patients on placebo and 6 patients on ustekinumab had been exposed to, but had not failed, biologics.

[b] The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.

[c] Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).
[d] Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
[e] Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).
[f] Corticosteroid-free clinical remission was defined as patients in clinical remission and not receiving corticosteroids at Week 44.
[g] p =<0.001
[h] p=0.004

Other Endpoints

Week 16 Responders to Ustekinumab Induction

Patients who were not in clinical response 8 weeks after induction with ustekinumab in UC-1 were not included in the primary efficacy analyses for Study UC-2; however, these patients were eligible to receive a 90 mg subcutaneous injection of ustekinumab at Week 8. Of these patients, 55/101 (54%) achieved clinical response eight weeks later (Week 16) and received ustekinumab 90 mg subcutaneously every 8 weeks during the UC-2 trial. At Week 44, there were 97/157 (62%) patients who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44

The proportion of patients achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among patients on ustekinumab and 40/172 (23%) in patients on placebo at Week 44. The relationship of histologic-endoscopic mucosal improvement, as defined in UC-2, at Week 44 to progression of disease or long-term outcomes was not evaluated in UC-2.

Endoscopic Normalization

Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At Week 8 in UC-1, endoscopic normalization was achieved in 25/322 (8%) of patients treated with ustekinumab and 12/319 (4%) of patients in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of patients treated with ustekinumab and in 32/175 (18%) of patients in placebo group.

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration (FDA), a single intravenous administration of ustekinumab (Stelara®) or ustekinumab-srlf (Imuldosa), or ustekinumab-aauz (Otulfi), or ustekinumab-ttwe (Pyzchiva®), or ustekinumab-aekn (Selarsdi), or ustekinumab-stba (Steqeyma), or ustekinumab-auub (Wezlana™) or ustekinumab-kfce (Yesintek™) may be considered medically necessary for the FDA labeled indications in adult patients 18 years and older with either: moderately to severely active Crohn's disease (CD); or moderately to severely active ulcerative colitis (UC). Intravenous administration of ustekinumab

(Stelara®) or its biosimilars is considered experimental, investigational and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J3357, J3358, J3490, J3590, Q5137, Q5138, Q9996, Q9997, Q9998

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
TBD	Document updated with literature review. The following change was added to Coverage: Revised coverage statements to include the biosimilars ustekinumab-srlf (Imuldosa), ustekinumab-aauz (Otulfi), ustekinumab-ttwe (Pyzchiva®), ustekinumab-aekn (Selarsdi), ustekinumab-stba (Steqeyma), and ustekinumab-kfce (Yesintek™). Added references 6-11.
07/15/2024	Document updated with literature review. The following change was made to Coverage: Revised coverage statements to include the biosimilar ustekinumab-auub (Wezlana). Added references 4 and 5. Title changed from Ustekinumab.
02/01/2024	Document updated with literature review. Coverage unchanged. References updated.
05/01/2023	Document updated with literature review. The following changes were made to the Coverage for clarification: 1) Added “A single intravenous administration of” to the following statement: A single intravenous administration of ustekinumab (Stelara®) is considered medically necessary for the treatment of: 2) Added “Intravenous administration of” to the following statement: Intravenous administration of ustekinumab (Stelara®) is considered experimental, investigational, and/or unproven for all other indications: 3) Added NOTE 3: Ustekinumab (Stelara®) shall not be used concurrently with other biologics used to treat the indications above. Please refer to the Description Section for a list of biological disease-modifying

	antirheumatic drugs (DMARDs). No new references added, references updated.
11/01/2021	Reviewed. No changes.
10/01/2020	New medical document originating from RX501.051. Ustekinumab (Stelara®) may be considered medically necessary for the FDA labeled indications for the treatment of adult patients 18 years and older with either moderately to severely active Crohn's disease (CD); or moderately to severely active ulcerative colitis. Stelara is considered experimental, investigational and/or unproven for all other indications.