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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 generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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.**

Coverage

NOTE 1: Stelara® and its associated biosimilars may be self-administered. For self-administered medications, please refer to the applicable pharmacy benefit plan.

A single intravenous administration of ustekinumab (Stelara®) or an associated biosimilars (see **NOTE 3**) **may be considered medically necessary** for the treatment of:

- Moderately to severely active Crohn's disease in individuals 2 years of age or older who are at least 10 kg; or
- Moderately to severely active ulcerative colitis in adults 18 years of age and older.

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

Intravenous administration of ustekinumab (Stelara®) or an associated biosimilar **is considered experimental, investigational, and/or unproven** for all other non-Food and Drug Administration approved indications.

NOTE 3: Stelara® (ustekinumab) biosimilars include:

- Imuldosa (ustekinumab-srlf)
- Otulfi (ustekinumab-aauz)
- Pyzchiva® (ustekinumab-ttwe)
- Selarsdi (ustekinumab-aekn)
- Starjemza (ustekinumab-hmny)
- Steqeyma (ustekinumab-stba)
- Wezlana™ (ustekinumab-auub)
- Yesintek™ (ustekinumab-kfce)

Policy Guidelines

Patients being treated with ustekinumab should not receive live vaccines. Bacille Calmette-Guerin 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 the patient.

Description

Crohn's Disease

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract. It belongs to a group of conditions known as inflammatory bowel diseases . 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 can affect any part of the GI tract, but most commonly affects the end of the small bowel (ileum) and the beginning of the colon. It can also affect the entire thickness of the bowel wall; and the inflammation may leave normal areas in between patches of diseased intestine. (11)

Ulcerative Colitis

Ulcerative colitis 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. Ulcerative colitis is the result of several factors that are not yet well understood. Abnormal immune response, genetics, microbiome, and environmental factors all contribute to ulcerative colitis. Research suggests that ulcerative colitis could be triggered by an interaction between a virus or bacterial infection in the colon and the body's immune response. (12)

Ustekinumab

Ustekinumab works by targeting immune system proteins called interleukin (IL)-12 and IL-23, which are thought to contribute to long-lasting inflammation in conditions like Crohn's disease, plaque psoriasis, psoriatic arthritis, and ulcerative colitis. By blocking interleukin, ustekinumab injection helps reduce inflammation and relieve symptoms of these conditions. Ustekinumab is usually administered as an injection under the skin (subcutaneous injection), and ustekinumab infusion is used for the first dose (induction) for Crohn's disease and ulcerative colitis. (10)

Regulatory

The U.S. Food and Drug Administration approvals for Stelara and its biosimilars are provided in Table 1.

Table 1. U.S. Food and Drug Administration Approval

Drug/Biosimilar	Year Approved	Indication(s)
Stelara (ustekinumab) (10)	2016 2019 2026	Adults and pediatric patients 2 years of age and older with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Wezlana (ustekinumab-auub) (2)	2023	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Imuldosa (ustekinumab-srlf) (3)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Otulfi (ustekinumab-aauz) (4)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Pyzchiva® (ustekinumab-ttwe) (5)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Selarsdi (ustekinumab-aekn) (6)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Steqeyma (usteminumab-stba) (8)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC

Yesintek™ (ustekinumab-kfce) (7)	2024	Adults with moderately to severely active CD and for the treatment of adults with moderately to severely active UC
Starjemza (ustekinumab-hmny) (9)	2025	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 is based on the U.S. Food and Drug Administration (FDA) labeled indications for ustekinumab (Stelara®) and associated biosimilars.

Adult Crohn's Disease (CD) (1-9)
Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical trials in adult subjects 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. Subjects in CD-1 had failed or were intolerant to treatment with one or more tumor necrosis factor (TNF) blockers, while subjects in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed treatment with a TNF blocker.

Trials CD-1 and CD-2
In trials CD-1 and CD-2, 1409 subjects 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, subjects 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 trial CD-1, subjects had failed or were intolerant to prior treatment with a TNF blocker: 29% subjects 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 subjects were receiving corticosteroids and 31% of the subjects were receiving immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]). The median baseline CDAI score was 319 in the ustekinumab approximately 6 mg/kg group and 313 in the placebo group.

In trial CD-2, subjects had failed or were intolerant to prior treatment with corticosteroids (81% of subjects), at least one immunomodulator (6-MP, AZA, MTX; 68% of patients), or both (49% of subjects). 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 subjects were receiving corticosteroids and 35% of the subjects 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 trials, a greater proportion of subjects 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 2 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in ustekinumab-treated subjects and continued to improve through Week 8.

Table 2. 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; CDAI: Crohn's Disease Activity Index; AZA: azathioprine; 6-MP: 6-mercaptopurine; MTX: methotrexate.
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 tumor necrosis factor (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] $p < 0.001$.

Trial CD-3

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

Table 3. Clinical Response and Remission in CD-3 (Week 44; 52 Weeks from Initiation of the Induction Dose)

	Placebo* N=131[a]	**90 mg 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 subjects who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
** Subjects 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] Subjects 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 subjects who received ustekinumab were corticosteroid-free and in clinical remission, compared to 30% of subjects in the placebo group.

At Week 0 of trial CD-3, 34/56 (61%) ustekinumab treated subjects who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these subjects were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) subjects were in clinical remission at Week 0 while 16/61 (26%) of these subjects were in remission at Week 44.

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

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

Pediatric Crohn's Disease (1-9)
The efficacy and safety of ustekinumab was evaluated in 101 pediatric patients aged 2 years to 17 years in a multi-center trial consisting of an open-label intravenous 8-week induction phase followed by randomization to one of two subcutaneous dosage regimens in a 44-week double-blind maintenance phase representing 52 weeks of therapy. Efficacy analyses were conducted in 93 patients with moderately to severely active Crohn's disease (NCT04673357).

Pediatric patients enrolled in the study had an inadequate response or were intolerant to treatment with oral corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) and/or prior biologic therapy, (TNF blockers or vedolizumab).

Of the 93 subjects included in the efficacy analyses, the mean age was 14 years (range 5 to 17 years), the median weight was 49 kg, and 39% were female. Additionally, 99% identified as not Hispanic or Latino and 1% as not reported; 89% identified as White, 8% as Asian, 2% as Black or African American, and 1% as not reported. The median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 and the median Simple Endoscopic Score for Crohn's Disease (SES-CD) was 12.

Patients received induction treatment with a single ustekinumab intravenous dose, of approximately 6 mg/kg (patients weighing 40 kg or more) or 250 mg/m^2 (patients weighing less than 40 kg, based on body surface area [BSA]), followed by a randomized double-blind subcutaneous maintenance regimen of 90 mg ustekinumab (patients weighing 40 kg or more) or 60 mg/m^2 ustekinumab (patients weighing less than 40 kg, based on BSA) every 8 weeks or another subcutaneous dosage regimen.

The recommended dosage for pediatric patients weighing 10 kg to less than 40 kg differs from the BSA-based dosage in this study. There are no anticipated clinically relevant differences in efficacy between the recommended and studied pediatric dosages of Ustekinumab.

The primary endpoint of the study was clinical remission at Week 52 (from initiation of induction) which was evaluated in the subset of patients who achieved clinical response at Week 8.

Efficacy Results
At Week 8, the proportion of patients who achieved clinical remission (defined as PCDAI score of ≤10) was 46% (43/93).

The proportion of patients in clinical response at Week 8, defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score ≤30, was 87% (81/93).

Of the 81 patients who received intravenous induction treatment and achieved clinical response or remission at Week 8, there were 39 patients who received the subcutaneous maintenance dosage described above every 8 weeks. Efficacy endpoints assessed at Week 52, including clinical response and/or remission (shown in Table 4), were assessed in this subset of patients.

Table 4. Proportion of Pediatric Patients 2 Years of Age and Older with Moderately to Severely Active Crohn's Disease Meeting Efficacy Endpoints at Week 52 (From Initiation of Induction) in a Clinical Trial

Endpoint	**90 mg or 60 mg/m^2 ustekinumab Every 8 Weeks[a] n/N (%) [95% CI]**
Clinical Remission[b]	20/39 (51%) [36%, 66%]
Clinical Response[c]	23/39 (59%) [43%, 73%]
Clinical Remission in Patients in Clinical Remission at Week 8[d]	17/21 (81%) [59%, 93%]

CI: confidence interval; PCDAI: Pediatric Crohn's Disease Activity Index.
[a] This subcutaneous dosage regimen followed 8 weeks after a single intravenous induction dose of approximately 6 mg/kg (patients weighing 40 kg or more) or 250 mg/m^2 (patients weighing less than 40 kg, based on body surface area [BSA]).
[b] Clinical remission is defined as PCDAI score ≤10.
[c] Clinical response is defined as reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score ≤30.
[d] Endpoint was evaluated in subjects 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.

At Week 52, the proportion of patients in endoscopic response, defined as a reduction in the SES-CD score of >50% or SES-CD score ≤ 2, in patients with a baseline SES-CD score of ≥ 3, was 26% (10/39). The proportion of patients achieving corticosteroid-free clinical remission defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week 52, was 49% (19/39).

Ulcerative Colitis (UC) (1-9)
Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical trials [UC-1 and UC-2 (NCT02407236)] in adult subjects 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 trial (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance trial (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, subjects had a median Mayo score of 9, with 84% of subjects having moderate disease (Mayo score 6-10) and 15% having severe disease (Mayo score 11-12).

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

Trial UC-1

In UC-1, 961 subjects 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. Subjects 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% of subjects were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% of subjects 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 subjects 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 subjects on placebo and 9 subjects 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 subjects.

Trial UC-2
The maintenance trial (UC-2) evaluated 523 subjects who achieved clinical response 8 weeks following the intravenous administration of either induction dose of ustekinumab in UC-1. These subjects 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 subjects in clinical remission at Week 44. The secondary endpoints included the proportion of subjects maintaining clinical response at Week 44, the proportion of subjects with endoscopic improvement at Week 44, the proportion of subjects with corticosteroid-free clinical remission at Week 44, and the proportion of subjects maintaining clinical remission at Week 44 among subjects who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in subjects 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**		**90 mg 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 subjects 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 subjects on placebo and 6 patients on ustekinumab had been exposed to, but had not failed, biologics.

[b] The placebo group consisted of subjects 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 subjects 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

Subjects 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 subjects were eligible to receive a 90 mg subcutaneous injection of ustekinumab at Week 8. Of these subjects, 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%) subjects who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44

The proportion of subjects achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among subjects on ustekinumab and 40/172 (23%) in subjects 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 subjects treated with ustekinumab and 12/319 (4%) of subjects in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of subjects treated with ustekinumab and in 32/175 (18%) of subjects in placebo group.

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 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, Q5098, Q5099, Q5100, Q5137, Q5138, Q5164, Q9996, Q9997, Q9998, Q9999

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. Prescribing Label: Stelara (ustekinumab) injection, for subcutaneous or intravenous use. April 2026. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed April 30, 2026).
2. Prescribing Label: Wezlana (ustekinumab-auub) injection, for subcutaneous or intravenous use. September 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed Jan. 5, 2026).
3. Prescribing Label: Imuldosa (ustekinumab-srlf) injection, for subcutaneous or intravenous use. November 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed Jan. 5, 2026).
4. Prescribing Label: Otulfi (ustekinumab-aauz) injection, for subcutaneous or intravenous use. Jan 2026. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed April 30, 2026).
5. Prescribing Label: Pyzchiva® (ustekinumab-ttwe) injection, for subcutaneous or intravenous use. November 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed Jan. 5, 2026).
6. Prescribing Label: Selarsdi (ustekinumab-aekn) injection, for subcutaneous or intravenous use. December 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed Jan. 5, 2026).
7. Prescribing Label: Yesintek™ (ustekinumab-kfce) injection, for subcutaneous or intravenous use. January 2026. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed April 30, 2026).
8. Prescribing Label: Steqeyma (ustekinumab-stba) injection, for subcutaneous or intravenous use. December 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed Jan. 5, 2026).
9. Prescribing Label: Starjemza (ustekinumab-hmny) injection, for subcutaneous or intravenous use. May 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed Jan. 5, 2026).

Other:

10. Stelara Approval History. Available at: https://www.drugs.com (accessed April 30, 2026).
11. Crohn's & Colitis Foundation. Overview of Crohn's Disease. Available at: https://www.crohnscolitisfoundation.org (accessed Jan. 6, 2026).
12. Crohn's & Colitis Foundation. Overview of Ulcerative Colitis. Available at: https://www.crohnscolitisfoundation.org (accessed Jan. 6, 2026).

Centers for Medicare & Medicaid Services

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 & Medicaid Services does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed 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**
7/21/2026	New medical document. Ustekinumab and associated biosimilars may be considered medically necessary when criteria in Coverage are met.