Stelara® (Ustekinumab)

Policy Number: CS2024D0045AB
Effective Date: March 1, 2024

Ü Instructions for Use

Table of Contents **Page**

Related Community Plan Policy
· Maximum Dosage and Frequency

Commercial Policy
· Stelara® (Ustekinumab)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Refer to the state's Medicaid clinical policy
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Ohio	Stelara® (Ustekinumab) (for Ohio Only)
Pennsylvania	Refer to the state's Medicaid clinical policy
Washington	Refer to the state's Medicaid clinical policy

Coverage Rationale

This policy refers to Stelara (ustekinumab) injection. Stelara (ustekinumab) for self-administered subcutaneous injection is obtained under the pharmacy benefit.

Stelara is proven and medically necessary for the treatment of:

Crohn's Disease

- Crohn's disease when all of the following criteria are met:[1]
  - o Diagnosis of moderately to severely active Crohn's disease; **and**
  - o One of the following:
    - § For **initial therapy**, **all** of the following:
      - – One of the following:
        - · History of failure to **one** of the following conventional therapies at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced

- Corticosteroids (e.g., prednisone, methylprednisolone, budesonide)
- 6-mercaptopurine (Purinethol)
- Azathioprine (Imuran)
- Methotrexate (Rheumatrex, Trexall)

or

- Patient has been previously treated with a biologic DMARD FDA-approved for the treatment of Crohn's disease [e.g., adalimumab, Cimzia (certolizumab), Skyrizi (risankizumab), Rinvoq (upadacitinib)]

and

- History of failure, contraindication or intolerance to **two** biologic DMARDs FDA-approved for the treatment of Crohn's disease (document drug, date, and duration of trial); **and**
- Stelara is to be administered as a single intravenous induction dose; **and**
- Stelara induction dosing is in accordance with the United States Food and Drug Administration (FDA) approved labeled dosing for Crohn's disease; **and**
- Patient is not receiving Stelara in combination with **either** of the following:
  - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]

  and
- Prescribed by or in consultation with a gastroenterologist; **and**
- Authorization will be for one induction dose

or

For **continuation of therapy**, **all** of the following:

- Documentation of positive clinical response; **and**
- Prescriber attestation that the patient or caregiver is not able to be trained or is physically unable to administer Stelara FDA labeled for self-administration; prescriber must submit explanation; **and**
- Stelara is to be subcutaneously administered 8 weeks after the initial intravenous dose; **and**
- Stelara continuation dosing is in accordance with the U.S. FDA approved labeled dosing for Crohn's disease; **and**
- Patient is not receiving Stelara in combination with **either** of the following:
  - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]

  and
- Authorization is for no more than 12 months

Plaque Psoriasis

- **Plaque psoriasis when all of the following criteria are met**:[1]
  - For **initial therapy**, **all** of the following:
    - Diagnosis of moderate to severe plaque psoriasis; **and**
    - **One** of the following:
      - **All** of the following:
        - Greater than or equal to 3% body surface area involvement, palmoplantar, facial, genital involvement, or severe scalp psoriasis; **and**
        - **One** of the following
          - **Both** of the following
            - History of failure to **one** of the following topical therapies, unless contraindicated or clinically significant adverse effects are experienced:
              - Corticosteroids (e.g., betamethasone, clobetasol, desonide)
              - Vitamin D analogs (e.g., calcitriol, calcipotriene)
              - Tazarotene
              - Calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
              - Anthralin
              - Coal tar

              and
            - History of failure to a 3 month trial of methotrexate at the maximally indicated dose, unless contraindicated or clinically significant adverse effects are experienced; **or**

- Patient has been previously treated with a biologic or targeted synthetic DMARD FDA-approved for the treatment of plaque psoriasis [e.g., adalimumab, Enbrel (etanercept), Cimzia (certolizumab), Orencia (abatacept), Skyrizi (risankizumab), Tremfya (guselkumab), Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), Ilumya (tildrakizumab), Otezla (apremilast)]

  and

  - History of failure, contraindication or intolerance to **two** biologic or targeted synthetic DMARDs FDA-approved for the treatment of plaque psoriasis (document drug, date, and duration of trial)

  or

  - Patient is currently on Stelara

  and

- Prescriber attestation that the patient or caregiver is not able to be trained or is physically unable to administer Stelara FDA labeled for self-administration; prescriber must submit explanation; **and**
- Stelara is initiated and titrated according to U.S. FDA labeled dosing for plaque psoriasis; **and**
- Patient is not receiving Stelara in combination with **any** of the following:
  - Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]
  - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

  and
- Prescribed by or in consultation with a dermatologist; **and**
- Initial authorization is for no more than 12 months

- For **continuation of therapy**, **all** of the following:
  - Documentation of positive clinical response; **and**
  - Prescriber attestation that the patient or caregiver is not able to be trained or is physically unable to administer Stelara FDA labeled for self-administration; prescriber must submit explanation; **and**
  - Stelara is initiated and titrated according to U.S. FDA labeled dosing for plaque psoriasis; **and**
  - Patient is not receiving Stelara in combination with **any** of the following:
    - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
    - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]
    - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

    and
  - Authorization is for no more than 12 months

Psoriatic Arthritis

- **Psoriatic arthritis when all of the following criteria are met**:[1]
  - For **initial therapy**, **all** of the following:
    - Diagnosis of psoriatic arthritis; **and**
    - **One** of the following:
      - History of failure to a 3 month trial of methotrexate at the maximally indicated dose, unless contraindicated or clinically significant adverse effects are experienced; **or**
      - Patient has been previously treated with a biologic or targeted synthetic DMARD FDA-approved for the treatment of psoriatic arthritis [e.g., adalimumab, Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Orencia (abatacept), Skyrizi (risankizumab), Tremfya (guselkumab), Cosentyx (secukinumab), Taltz (ixekizumab), Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Otezla (apremilast)]; **or**
      - Patient is currently on Stelara

      and
    - **One** of the following:
      - History of failure, contraindication or intolerance to **two** biologic or targeted synthetic DMARDs FDA-approved for the treatment of psoriatic arthritis (document drug, date, and duration of trial):

      or

      - Patient is currently on Stelara

      and
    - Stelara is initiated and titrated according to U.S. FDA labeled dosing for psoriatic arthritis; **and**

- § Prescriber attestation that the patient or caregiver is not able to be trained or is physically unable to administer Stelara FDA labeled for self-administration; prescriber must submit explanation; **and**
- § Patient is not receiving Stelara in combination with **any** of the following:
  - – Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - – Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]
  - – Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

  and
- § Prescribed by or in consultation with **one** of the following:
  - – Rheumatologist
  - – Dermatologist

  and
- § Initial authorization is for no more than 12 months

o For **continuation of therapy**, **all** of the following:
- § Documentation of positive clinical response; **and**
- § Prescriber attestation that the patient or caregiver is not able to be trained or is physically unable to administer Stelara FDA labeled for self-administration; prescriber must submit explanation; **and**
- § Stelara is initiated and titrated according to U.S. FDA labeled dosing for psoriatic arthritis; **and**
- § Patient is not receiving Stelara in combination with **any** of the following:
  - – Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - – Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]
  - – Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

  and
- § Authorization is for no more than 12 months

Ulcerative Colitis

- **Ulcerative colitis when all of the following criteria are met:**[1]
  - o Diagnosis of moderately to severely active ulcerative colitis; **and**
  - o **One** of the following:
    - § Patient has had prior or concurrent inadequate response to a therapeutic course of oral corticosteroids and/or immunosuppressants (e.g., azathioprine, 6-mercaptopurine); **or**
    - § Patient has been previously treated with a biologic or targeted synthetic DMARD FDA-approved for the treatment of ulcerative colitis as documented by claims history or submission of medical records (Document drug, date, and duration of therapy) [e.g., adalimumab, Simponi (golimumab), Xeljanz (tofacitinib), Rinvoq (upadacitinib)] ; **or**
    - § Patient is currently on Stelara

    and
  - o History of failure, contraindication or intolerance to ONE biologic or targeted synthetic DMARD FDA-approved for the treatment of ulcerative colitis (document drug, date, and duration of trial); **and**
  - o **One** of the following:
    - § **Initial therapy:**
      - – Stelara is to be administered as a single intravenous induction dose; **and**
      - – Stelara induction dosing is in accordance with the U.S. FDA approved labeled dosing for ulcerative colitis; **and**
      - – Patient is not receiving Stelara in combination with **either** of the following:
        - · Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
        - · Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]

        and
      - – Prescribed by or in consultation with a gastroenterologist; **and**
      - – Authorization will be for one induction dose
    - § **Continuation of therapy**:
      - – Documentation of positive clinical response; **and**
      - – Prescriber attestation that the patient or caregiver is not able to be trained or is physically unable to administer Stelara FDA labeled for self-administration; prescriber must submit explanation; **and**
      - – Stelara is to be subcutaneously administered 8 weeks after the initial intravenous dose; **and**

- Stelara continuation dosing is in accordance with the U.S. FDA approved labeled dosing for ulcerative colitis; **and**
- Patient is not receiving Stelara in combination with **either** of the following:
  - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)][16]

  and
- Authorization is for no more than 12 months

Stelara is unproven and not medically necessary for the treatment of:

- Ankylosing spondylitis
- Multiple sclerosis

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3357	Ustekinumab, for subcutaneous injection, 1 mg
J3358	Ustekinumab, for intravenous injection, 1 mg

Diagnosis Code	Description
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications

Diagnosis Code	Description
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.219	Ulcerative (chronic) proctitis with unspecified complications
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.319	Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.519	Left sided colitis with unspecified complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.819	Other ulcerative colitis with unspecified complications
K51.90	Ulcerative colitis, unspecified, without complications

Diagnosis Code	Description
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified with intestinal obstruction
K51.913	Ulcerative colitis, unspecified with fistula
K51.914	Ulcerative colitis, unspecified with abscess
K51.918	Ulcerative colitis, unspecified with other complication
K51.919	Ulcerative colitis, unspecified with unspecified complications
K51.40	Inflammatory polyps of colon without complications
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.419	Inflammatory polyps of colon with unspecified complications
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.2	Acrodermatitis continua
L40.3	Pustulosis palmaris et plantaris
L40.4	Guttate psoriasis
L40.50	Arthropathic psoriasis, unspecified
L40.51	Distal interphalangeal psoriatic arthropathy
L40.52	Psoriatic arthritis mutilans
L40.53	Psoriatic spondylitis
L40.54	Psoriatic juvenile arthropathy
L40.59	Other psoriatic arthropathy
L40.8	Other psoriasis
L40.9	Psoriasis, unspecified

Background

Stelara is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 naturally occurring cytokines. IL-12 and IL-23 are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.[1]

Clinical Evidence

Proven

Ulcerative Colitis

Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or immunomodulator therapy. The 8-week intravenous induction study was followed by the 44-week subcutaneous randomized withdrawal maintenance study for a total of 52 weeks of therapy.[1,21]

A total of 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 (523 patients) who had a response to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned again to receive subcutaneous maintenance

injections of 90 mg of ustekinumab [either every 12 weeks (172 patients) or every 8 weeks (176)] or placebo (175) for 44 weeks. The primary end point in the induction trial (week 8) and the maintenance trial (week 44) was clinical remission [defined as a total score of ≤ 2 on the Mayo scale (range, 0 to 12, with higher scores indicating more severe disease) and no sub score > 1 (range, 0 to 3) on any of the four Mayo scale components]. The percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg (15.6%) or 6 mg per kilogram (15.5%) was significantly higher than that among patients who received placebo (5.3%) ($P < 0.001$ for both comparisons). Among patients who had a response to induction therapy with ustekinumab and underwent a second randomization, the percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks (38.4%) or every 8 weeks (43.8%) than among those assigned to placebo (24.0%) ($P = 0.002$ and $P < 0.001$, respectively). The incidence of serious adverse events with ustekinumab was similar to that with placebo. The proportion of patients achieving histologic-endoscopic mucosal improvement during maintenance treatment 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 at Week 44 to progression of disease or long-term outcomes was not evaluated. At Week 44, endoscopic normalization was achieved in 51/176 (29%) of patients treated with ustekinumab and in 32/175 (18%) of patients in placebo group. The authors concluded that ustekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe ulcerative colitis.[1,21]

Crohn's Disease

Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease. There were two 8-week intravenous induction studies followed by a 44-week subcutaneous randomized withdrawal maintenance study representing 52 weeks of therapy.[1,17]

In the two induction studies, 1409 patients were randomized, and 1368 (CD-1, n = 741; CD-2, n = 628) were included in the final efficacy analysis. Induction of clinical response at Week 6 and clinical remission at Week 8 were primary endpoints. In both studies, patients were randomized to receive a single intravenous administration of ustekinumab at approximately 6 mg/kg, placebo, or 130 mg. In the first study, 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 this study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the ustekinumab approximately 6 mg/kg group and 313 in the placebo group.[1,17,18]

In the second induction study, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator; (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. The median baseline CDAI score was 286 in the ustekinumab and 290 in the placebo group.[1,17,18]

In both of the induction studies, a greater proportion of patients treated with ustekinumab 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 ustekinumab treated patients and continued to improve through Week 8.[1,17,18]

The maintenance study evaluated 388 patients who achieved clinical response (≥ 100 point reduction in CDAI score) at Week 8 of induction with ustekinumab in either of the induction studies. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks or placebo for 44 weeks.[1,17,18]

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 this study, 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 this study, 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; however, these patients were eligible to receive a 90 mg subcutaneous injection of ustekinumab upon entry into the maintenance study. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.1,17,18

Plaque Psoriasis

A phase 3, multi-center, double-blind, placebo-controlled, randomized study evaluated the safety and efficacy of ustekinumab in patients age 12 to 17 years who had moderate-to-severe psoriasis.[17] Patients (n = 110) were randomly assigned (2:2:1:1) ratio to ustekinumab [SD; 0.75 mg/kg (≤ 60 kg), 45 mg (> 60 - ≤ 100 kg), and 90 mg (> 100 kg)] or half-standard dosing [HSD; 0.375 mg/kg (≤ 60 kg), 22.5 mg (> 60 - ≤ 100 kg), and 45 mg (> 100 kg)] at weeks 0 and 4 and every 12 weeks or placebo at weeks 0 and 4 with crossover to ustekinumab SD or HSD at weeks 12 and 16 and thereafter every 12 weeks through week 40. At week 8, patients with a PASI increase ≥ 50% from baseline were eligible to commence treatment with moderate-to-high potency topical steroid preparations through week 12. The primary endpoint was the proportion of patients with a Physician's Global Assessment (PGA) 0/1 at week 12. Major secondary endpoints were the proportions of patients achieving at least 75% improvement in PASI (PASI 75) and at least 90% improvement in PASI (PASI 90) at week 12 and the change from baseline in Children's' Dermatology Life Quality Index (CDLQI) at week 12. Assessments were performed through week 52. At week 12, the proportions of patients achieving PGA 0/1 were significantly greater in the HSD (67.6%) and SD (69.4%) groups versus placebo (5.4%; P < 0.001 for both dose groups). Approximately one-third of patients in each ustekinumab group achieved PGA 0/1 at week 4. Significantly greater proportions of patients in the HSD (32.4%) and SD (47.2%) groups achieved a PGA of 0 at week 12 compared to placebo (2.7%, bot P < 0.001). Significantly greater proportions of patients receiving ustekinumab achieved PASI 75 (HSD, 78.4%; SD, 80.6%; placebo, 10.8%; P < 0.001) or PASI 90 (HSD, 54.1%; SD, 61.1%; placebo, 5.4%; P < 0.001). Additionally, 21.6% of patients in the HSD group and 38.9% in the SD group achieved a PASI score of 0 (cleared) at week 12 compared with 2.7% in the placebo group (P = .014 and P < 0.001, respectively). The treatment effect of both the HSD and SD of ustekinumab through week 12 for patients < 60 kg was consistent with that observed in patients > 60 kg to ≤ 100 kg. Placebo patients who crossed over to ustekinumab at week 12, PASI 75 response rates increased by week 16 and were maintained through week 52. The proportions of patients achieving PGA 0/1, PASI 75, or PASI 90 after crossover were generally similar to those observed in patients who started ustekinumab at baseline. Through week 40, all 110 patients received at least 1 injection of ustekinumab; among these, 81.8% reported an adverse event (AE) through week 60. By week 12, only one serious AE (SAE) was reported in the HSD group. After week 12, 5 additional singular SAEs were reported (total, 6; HSD, 5; SD, 1) through week 60. The investigators concluded that ustekinumab, in patients 12 to 17 years, the standard dose provided response comparable to that in adults with no unexpected adverse events through 1 year.

Griffiths et al. conducted a blinded, multi-center, head-to-head comparison of ustekinumab versus etanercept in the treatment of moderate-to-severe plaque psoriasis.[11] Patients (n = 903) were randomly assigned in a 3:5:5 ratio to receive subcutaneous injections of ustekinumab 45 mg (n = 209) at weeks 0 and 4, ustekinumab 90 mg (n = 347) at weeks 0 and 4, or etanercept 50 mg (n = 347) twice weekly for 12 weeks. The primary end point was the proportion of patients with at least 75% improvement in the PASI index at week 12. A secondary end point was the proportion with cleared or minimal disease on the basis of the physician's global assessment. At week 12, a total of 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg of ustekinumab had at least 75% improvement in the PASI score, as compared with 56.8% of those who received high-dose etanercept (P = 0.01 and P < 0.001, respectively). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.6% of patients who received 90 mg of ustekinumab had cleared or minimal disease according to the physician's global assessment, as compared with 49.0% of those who received etanercept (P < 0.001 for both comparisons). Among patients who did not have a response to etanercept, 48.9% had at least 75% improvement in the PASI within 12 weeks after crossover to ustekinumab. One or more adverse events occurred through week 12 in 66.0% of patients who received 45 mg of ustekinumab and 69.2% of patients who received 90 mg of ustekinumab and in 70.0% who received etanercept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety patterns were similar before and after crossover from etanercept to ustekinumab. The investigators concluded that ustekinumab at a dose of 45 or 90 mg had superior efficacy to high-dose etanercept over a 12-week period in patients with psoriasis.

Unproven

Ankylosing Spondylitis

Three randomized, placebo-controlled studies evaluated the safety and efficacy of ustekinumab for the treatment of patients with axial spondyloarthritis (SpA).[22] The first two studies included patients with radiographic axial SpA [anti-tumor necrosis

factor (anti-TNF)-naive patients and patients with an inadequate response or intolerance to anti-TNF, respectively], while the third study, patients had nonradiographic axial SpA. In all of the studies, patients were randomly assigned (1:1:1) to receive subcutaneous ustekinumab at 45 mg or 90 mg or placebo up to 24 weeks, after which placebo-treated patients were re-randomized to receive ustekinumab at 45 mg or 90 mg. The primary end point in studies 1 and 2 was the proportion of patients who met the Assessment of SpondyloArthritis international Society criteria for 40% improvement in disease activity (achieved an ASAS40 response). The primary end point in study 3 was the proportion of patients who achieved an ASAS20 response. Other disease activity and safety measures were also evaluated. A week 24 analysis of study 1 was preplanned to determine continuation of studies 2 and 3. For study 1, the primary and major secondary end points were not met, and the study was discontinued. As a result, studies 2 and 3 were prematurely discontinued before they were fully enrolled. For all 3 studies, neither ustekinumab dose group demonstrated clinically meaningful improvement over placebo on key efficacy end points. The proportion of patients experiencing adverse events in the ustekinumab groups was consistent with that in previous studies. The investigators concluded that the efficacy of ustekinumab in the treatment of axial SpA was not demonstrated.

Multiple Sclerosis

Kasper et al. conducted a phase I, double-blind, placebo-controlled, sequential dose escalation study in 20 subjects with multiple sclerosis (MS).[8] Subjects were randomized (4:1) to receive a single subcutaneous injection of either ustekinumab (0.3, 0.75, 1.5, and 3 mg/kg) or placebo. Clinical and laboratory evaluations were performed through 16 weeks following administration. Single subcutaneous administrations of ustekinumab in this first study of relapsing MS were generally well tolerated. Adverse events were generally mild or moderate, with no apparent dose-related trends. There was a large degree of variability in T2 lesion volume and total number of gadolinium-positive lesions, both unaffected by dose escalation. Three relapses of MS occurred in two placebo-treated subjects. Over the range of single doses studied, the median Tmax ranged from 9.0 to 16.5 days, and the median $T_{1/2}$ ranged from 20.2 to 30.9 days. The authors concluded that safety of ustekinumab in MS needs to be tested in a study of longer duration and involving a larger cohort of subjects.

In a phase II, multicenter, randomized, double-blind, placebo-controlled trial, Segal et al. studied repeated injections of ustekinumab in patients (n = 249) with relapsing-remitting multiple sclerosis (RRMS).[9] Subjects aged 18-65 years were assigned to one of five groups: placebo (n = 49) or four different ustekinumab dosages (n = 50 for all) at weeks 0, 1, 2, 3, 7, 11, 15, and 19. Ustekinumab doses were 27 mg, 90 mg q8w, 90 mg, or 180 mg; the 90 mg q8w dosage group received placebo substitute at weeks 7 and 15. The primary endpoint was the cumulative number of new gadolinium-enhancing T1-weighted lesions on serial cranial MRI through week 23. Patients were followed up through week 37. In the intent to treat analysis, ustekinumab treatment did not show a significant reduction in the primary endpoint for any dosage groups versus placebo. At week 37, adverse events occurred in 38 (78%) placebo-treated patients and 170 (85%) ustekinumab-treated patients, with infections most commonly reported. Serious adverse events occurred in one (2%) placebo-treated patient and six (3%) ustekinumab-treated patients. Malignant diseases were reported in two patients shortly after the initiation of ustekinumab treatment; both patients were withdrawn from the trial and given appropriate treatment, which resulted in complete remission. No serious infections, cardiovascular events, or exacerbation of demyelinating events occurred. A dose-dependent increase in serum concentrations of ustekinumab was recorded. The investigators concluded that ustekinumab is generally well tolerated but does not show efficacy in reducing the cumulative number of gadolinium-enhancing T1-weighted lesions in multiple sclerosis.

Professional Societies

Crohn's Disease

The American College of Gastroenterology published their clinical practice guidelines for the management of adults with Crohn's disease in 2018. In regard to ustekinumab, the guidelines recommend:

- Moderate-to-Severe Disease/Moderate-to-High-Risk Disease:
  - Ustekinumab should be given for moderate-to-severe Crohn's disease patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors (strong recommendation, high level of evidence)
- Maintenance Therapy of Luminal Crohn's Disease:
  - Ustekinumab should be use for maintenance of remission of ustekinumab-induced response of Crohn's disease (conditional recommendation, moderate level of evidence)

Plaque Psoriasis

In 2019, the American Academy of Dermatology and the National Psoriasis Foundation published updated treatment guidelines for the management and treatment of psoriasis with biologic therapies. In regards to ustekinumab, the guidelines state:

- Ustekinumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis
- The recommended starting doses of ustekinumab are as follows:
  - For patients weighing ≤ 100 kg, 45 mg administered subcutaneously initially and 4 wk. later, followed by 45 mg administered subcutaneously every 12 wk
  - For patients weighing > 100 kg, 90 mg administered subcutaneously initially and 4 wk. later, followed by 90 mg administered subcutaneously every 12 wk
- The recommended alternate dosage for ustekinumab is administered at higher doses (90 mg instead of 45 mg in patients weighing ≥ 100 kg) or at a greater frequency of injection (e.g., every 8 wk. in its maintenance phase) for those with an inadequate response to standard dosing
- Ustekinumab can be used as monotherapy for adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (plaque type palmoplantar psoriasis)
- Ustekinumab can be recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis affecting the nails
- Ustekinumab can be used as monotherapy for use in adult patients with moderate-to severe plaque psoriasis affecting the scalp
- Ustekinumab can be used as monotherapy for use in adult patients with other subtypes (palmoplantar, pustular, or erythrodermic) of moderate-to-severe plaque psoriasis. There is limited evidence for its use in inverse and guttate psoriasis
- Ustekinumab is recommended as a monotherapy treatment option for use in adult patients with plaque psoriasis of any severity when associated with psoriatic arthritis
- Combination of ustekinumab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults
- Ustekinumab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis
- Ustekinumab may be combined with methotrexate to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults
- Ustekinumab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults
- Ustekinumab may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults
- Ustekinumab may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults

Psoriatic Arthritis

In 2018, the American College of Rheumatology and the National Psoriasis Foundation published treatment guideline for the treatment of psoriatic arthritis. In regards to psoriatic arthritis (PsA) and anti-IL-12/23p40 antibodies, the guidelines state:

- Recommendations for the initial treatment of patients with active psoriatic arthritis who are oral small molecule (OSM)-and other treatment–naive:
  - Treat with a TNFi biologic over an IL-12/23i biologic
    - Conditional recommendation based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has severe psoriasis, prefers less frequent drug administration, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease
  - Treat with an OSM over an IL-12/23i biologic
    - Conditional recommendation based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD and/or severe psoriasis and/or severe PsA or prefers less frequent drug administration
  - Treat with an IL-17i biologic over an IL-12/23i biologic
    - Conditional recommendation based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration
- Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an OSM:
  - Switch to a TNFi biologic over an IL-12/23i biologic

        - § Conditional recommendation based on moderate-quality evidence; may consider an IL-12/23i if the patient has severe psoriasis and/or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration
    - o Switch to an IL-17i biologic over an IL-12/23i biologic
        - § Conditional recommendation based on moderate-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration
    - o Switch to an IL-12/23i biologic over a different OSM
        - § Conditional recommendation based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis
    - o Switch to an IL-12/23i biologic over abatacept
        - § Conditional recommendation based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections
    - o Switch to an IL-12/23i biologic over tofacitinib
        - § Conditional recommendation based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy
    - o Switch to an IL-12/23i biologic monotherapy over MTX and an IL-12/23i biologic combination therapy
        - § Conditional recommendation based on very-low-quality evidence; may consider MTX and an IL-12/
        - § 23i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy)
- Recommendations for treatment of patients with active psoriatic arthritis despite treatment with a TNFi biologic, as monotherapy or in combination with MTX:
    - o Switch to a different TNFi biologic over switching to an IL-12/23i biologic
        - § Conditional recommendation based on low-quality evidence; may consider an IL-12/23i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect or prefers less frequent drug administration
    - o Switch to an IL-17i biologic over switching to an IL-12/23i biologic
        - § Conditional recommendation based on low-quality evidence; may consider an IL-12/23i if the patient has IBD or if the patient prefers less frequent drug administration
    - o Switch to an IL-12/23i biologic over abatacept
        - § Conditional recommendation based on of low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections
    - o Switch to an IL-12/23i biologic over tofacitinib
        - § Conditional recommendation based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy
    - o Switch to an IL-12/23i biologic monotherapy over switching to an IL-12/23i biologic and MTX combination therapy
        - § Conditional recommendation based on very-low-quality evidence; may consider switching to an IL-12/
        - § 23i biologic and MTX combination therapy if the patient has severe psoriasis
- In adult patients with active PsA despite treatment with a TNFi biologic and MTX combination therapy:
    - o Switch to IL-12/23i biologic monotherapy over IL-12/23i biologic and MTX combination therapy
        - § Conditional recommendation based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work

Ulcerative Colitis

In 2020, the American Gastroenterological Association (AGA) published a clinical practice guideline on the management of moderate to severe ulcerative colitis. In regard to ustekinumab, the guidelines recommend:

- In adult outpatients with moderate-severe ulcerative colitis, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab over no treatment. (Strong recommendation, moderate quality evidence)
- In adult outpatients with moderate-severe ulcerative colitis who have previously been exposed to infliximab, particularly those with primary non-response, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab for induction of remission. (Conditional recommendation, low quality evidence)

- In adult outpatients with active moderate-severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNFα antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for induction of remission. (Conditional recommendation, low quality evidence)
- In adult outpatients with moderate-severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNFα antagonists, vedolizumab or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission. (No recommendation, knowledge gap)
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy. (Conditional recommendation, low quality evidence)
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than thiopurine monotherapy. (Conditional recommendation, low quality evidence)
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates. (Conditional recommendation, very low quality evidence)
- In adult outpatients with moderate-severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-aminosalicylates for induction and maintenance of remission. (Conditional recommendation, very low quality evidence)

The American College of Gastroenterology published their guidelines for the management of adults with ulcerative colitis in 2019. The ACG does not address the use ustekinumab for the induction or maintenance of remission in patients with moderately to severely active ulcerative colitis.

Technology Assessments

A 2020 Cochrane review was published to compare the efficacy and safety of conventional systemic agents, small molecules, and biologics for patients with moderate to severe psoriasis.[24] The technical assessment also sought to provide a ranking of these treatments according to their efficacy and safety. The assessment included 140 studies (31 new studies for the update) in our review (51,749 randomized participants, 68% men, mainly recruited from hospitals). Nineteen treatments were assessed. At class level, in terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents. At drug level, in terms of reaching PASI 90, infliximab, all of the anti-IL17 drugs (ixekizumab, secukinumab, bimekizumab and brodalumab) and the anti-IL23 drugs (risankizumab and guselkumab, but not tildrakizumab) were significantly more effective in reaching PASI 90 than ustekinumab and 3 anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Adalimumab and ustekinumab were significantly more effective in reaching PASI 90 than certolizumab and etanercept. There was no significant difference between tofacitinib or apremilast and between two conventional drugs: ciclosporin and methotrexate. The network meta-analysis also showed that infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab outperformed other drugs when compared to placebo in reaching PASI 90. The authors review showed that compared to placebo, the biologics infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab were the best choices for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of moderate- to high-certainty evidence (low-certainty evidence for bimekizumab).

In their 2019 update to the 2016 Cochrane review, the efficacy and safety of anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease (CD) was assessed. The authors included randomized controlled trials in which monoclonal antibodies against IL-12/23p40 were compared to placebo or another active comparator in participants with quiescent CD. The review evaluated three randomized controlled trials (646 participants). The authors concluded that moderate-certainty evidence suggests that ustekinumab is probably effective for the maintenance of clinical remission and response in people with moderate to severe CD in remission without an increased risk of adverse events (high-certainty evidence) or serious adverse events (moderate-certainty evidence) relative to placebo. The effect of briakinumab on maintenance of clinical remission and response in people with moderate to severe Crohn's disease in remission was uncertain as the certainty of the evidence was low.[20]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Stelara is a human interleukin-12 and -23 antagonist indicated for the treatment of:

- Adult patients (18 years or older) with:[1]
  - Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
  - Active psoriatic arthritis, alone or in combination with methotrexate
  - Moderately to severely active Crohn's disease
  - Moderately to severely active ulcerative colitis
- Adolescent patients (6 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and active psoriatic arthritis

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Policy History/Revision Information

Date	Summary of Changes
03/01/2024	**Coverage Rationale** • Revised coverage criteria: ***Crohn's Disease*** o Updated list of examples of biologic DMARDs the patient has been previously treated with for Crohn's disease: § Added: – Rinvoq (upadacitinib) – Skyrizi (risankizumab) § Replaced "Humira (adalimumab)" with "adalimumab" ***Plaque Psoriasis*** o Updated list of examples of biologic or targeted synthetic DMARDs the patient has been previously treated with for plaque psoriasis: § Added: – Cosentyx (secukinumab) – Enbrel (etanercept)

Date	Summary of Changes
	– Ilumya (tildrakizumab) – Orencia (abatacept) – Siliq (brodalumab) – Taltz (ixekizumab) § Replaced “Humira (adalimumab)” with “adalimumab” ***Psoriatic Arthritis*** o Updated list of examples of biologic or targeted synthetic DMARDs the patient has been previously treated with for psoriatic arthritis: § Added: – Cosentyx (secukinumab) – Enbrel (etanercept) – Olumiant (baricitinib) – Orencia (abatacept) – Rinvoq (upadacitinib) – Skyrizi (risankizumab) – Taltz (ixekizumab) § Replaced “Humira (adalimumab)” with “adalimumab” ***Ulcerative Colitis*** o Updated list of examples of biologic or targeted synthetic DMARDs the patient has been previously treated with for ulcerative colitis; replaced “Humira (adalimumab)” with “adalimumab” o Added criterion to allow coverage when the patient is currently on Stelara **Supporting Information** • Archived previous policy version CS2023D0045AA

Instructions for Use

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