Medical Policy Bulletin

Title:
Ustekinumab (Stelara®)
Policy #:
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This Medical Policy Bulletin document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy Bulletin will be reviewed regularly and be updated as scientific and medical literature becomes available. For more information on how Medical Policy Bulletins are developed, go to the Policy Types and Descriptions section of this Medical Policy Web site.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's contract.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

INITIAL THERAPY WITH USTEKINUMAB (STELARA)

CROHN'S DISEASE AND ULCERATIVE COLITIS
Ustekinumab (Stelara) is considered medically necessary and, therefore, covered for the treatment of individuals with moderately to severely active Crohn's disease or moderately to severely active ulcerative colitis when both of the following criteria and the Dosing and Frequency Requirements listed below are met:

- The individual is at least 18 years of age.
- There is documentation of failure, contraindication, or intolerance to a trial of one of the following:
  - Immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate)
  - Corticosteroids (e.g., budesonide [Entocort EC], prednisone, hydrocortisone, methylprednisolone)
  - Biologic therapy (e.g., certolizumab [Cimzia], adalimumab [Humira], infliximab [Remicade]), vedolizumab [Entyvio])

IMMUNE-CHECKPOINT INHIBITOR-RELATED TOXICITY MANAGEMENT
Ustekinumab (Stelara) is considered medically necessary and, therefore, covered for the management of the following autoimmune-like toxicities (also known as immune-related adverse events), when other etiologies have been ruled out and any of the following criteria and the Dosing and Frequency Requirements listed below are met:

- Mild (Grade 1) diarrhea or colitis if persistent or progressive symptoms after standard symptomatic treatments and positive lactoferrin/calprotectin
- Infliximab-and/or vedolizumab-refractory moderate (Grade 2) or severe (Grade 3-4) diarrhea or colitis

PLAQUE PSORIASIS

Ustekinumab (Stelara) for subcutaneous injection is considered medically necessary and, therefore, covered for the treatment of individuals with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, when both of the following criteria and the Dosing and Frequency Requirements listed below are met:

- The individual is at least 6 years of age.
- There is documentation of failure, contraindication, or intolerance to a trial of at least one of the following:
    - Topical steroids
    - Topical nonsteroids (e.g., topical calcipotriene [Dovonex], topical anthralin, topical retinoids [Tazorac])
    - Topical immune modulators (e.g., Elidel, Protopic)
    - Methotrexate (MTX) (e.g., Trexall, Rheumatrex)
    - Retinoids (e.g., acitretin [Soriatane])
    - Cyclosporine (e.g., Neoral, Gengraf)

PSORIATIC ARTHRITIS

Ustekinumab (Stelara) for subcutaneous injection is considered medically necessary and, therefore, covered when used alone or in combination with methotrexate (MTX) for the treatment of individuals with active psoriatic arthritis when both of the following criteria and the Dosing and Frequency Requirements listed below are met:

- The individual is at least 6 years of age.
- Documented failure, contraindication, or intolerance to a trial of at least one disease-modifying antirheumatic drugs (DMARDs) that include but are not limited to the following:
    - Sulfasalazine (e.g., Azulfidine)
    - Azathioprine (e.g., Imuran)
    - Hydroxychloroquine
    - Cyclosporine (e.g., Neoral, Gengraf)
    - Methotrexate (e.g., Trexall, Rheumatrex)
    - Anti-tumor necrosis factor agents

CONTINUATION THERAPY WITH USTEKINUMAB (STELARA)

Continuation therapy is considered medically necessary and, therefore, covered when the individual has met the coverage criteria for Initial Therapy, and the treatment with ustekinumab (Stelara) resulted in documented improvement of symptoms or functions of affected areas.

DOSING AND FREQUENCY OF ADMINISTRATION

The following dosage and frequency information was taken from the Prescribing Information for this product at the time the policy was being developed:

CROHN'S DISEASE, ULCERATIVE COLITIS, AND IMMUNE-CHECKPOINT INHIBITOR-RELATED TOXICITY MANAGEMENT (DIARRHEA, COLITIS)

- For initial intravenous infusion:
    - For persons whose weight is up to 55 kg, the recommended dose is 260 mg (2 vials).
    - For persons whose weight is more than 55 kg to 85 kg, the recommended dose is 390 mg (3 vials).
    - For persons whose weight is more than 85 kg, the recommended dose is 520 mg (4 vials).
- For subcutaneous injection as maintenance treatment:
    - The recommended dose is 90 mg 8 weeks after the initial intravenous dose, then every 8 weeks thereafter (for immune-checkpoint inhibitor-related toxicities, for a maximum of 3 maintenance doses).

PSORIASIS: subcutaneous injection

Adults:

- For persons whose weight is 100 kg (220 lbs) or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For persons whose weight is more than 100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Pediatrics 6-17 years of age:

- For persons whose weight is less than 60 kg (132 lbs), the recommended dose is 0.75 mg/kg initially, 4 weeks later, followed by 0.75 mg/kg every 12 weeks.
- For persons whose weight is 60 kg to 100 kg (132 to 220 lbs), the recommended dose is 45 mg initially, 4 weeks later, followed by 45 mg every 12 weeks.

- For persons whose weight is more than 100 kg (220 lbs), the recommended dose is 90 mg initially, 4 weeks later, followed by 90 mg every 12 weeks.

PSORIATIC ARTHRITIS: subcutaneous injection
Adults:

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For persons with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Pediatrics 6-17 years of age:

- For persons whose weight is less than 60 kg (132 lbs), the recommended dose is 0.75 mg/kg initially, 4 weeks later, followed by 0.75 mg/kg every 12 weeks.
- For persons whose weight is 60 kg (132 lbs) or more, the recommended dose is 45 mg initially, 4 weeks later, followed by 45 mg every 12 weeks.
- For persons whose weight is more than 100 kg (220 lbs) with co-existent moderate-to severe plaque psoriasis, the recommended dose is 90 mg initially, 4 weeks later, followed by 90 mg every 12 weeks.

EXPERIMENTAL/INVESTIGATIONAL

All other uses of ustekinumab (Stelara) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of ustekinumab (Stelara). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of ustekinumab (Stelara) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the precertification process. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for ustekinumab (Stelara).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of ustekinumab (Stelara) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

Individuals should not be receiving concurrent therapy with any other biologic disease-modifying antirheumatic drug (DMARD) (i.e., anti-tumor necrosis factor agents) while receiving ustekinumab (Stelara).

After proper training in subcutaneous injection technique, an individual may self-inject with ustekinumab (Stelara) if a professional provider determines that it is appropriate. Individuals should be instructed to follow the directions provided in the Medication Guide.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, ustekinumab (Stelara) is covered under the medical benefits of the Company's products when the medical necessity criteria and Dosing and Frequency Requirements listed in this medical policy are met. Ustekinumab (Stelara) for subcutaneous injection may be available for coverage under any applicable pharmacy benefit. Individual benefits must be verified.

Ustekinumab (Stelara) may be available under the member's medical benefits through the Direct Ship Injectables Program.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Ustekinumab (Stelara) received FDA approval on September 25, 2009 for the treatment of adults (18 years or older) with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Supplemental approvals for ustekinumab (Stelara) have since been issued by the FDA for the treatment of psoriatic arthritis, Crohn's disease, and ulcerative colitis.

PEDIATRIC USE

The safety and effectiveness of ustekinumab (Stelara) in pediatric individuals for the treatment of Crohns' disease and ulcerative colitis have not been evaluated.

The safety and effectiveness of ustekinumab (Stelara) have been established in pediatric individuals 6 to 17 years old with moderate to severe plaque psoriasis. Use of ustekinumab (Stelara) in adolescents this age group is supported by evidence from a multicenter, randomized, 60-week trial that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older. Use of ustekinumab (Stelara) in children 6 to 11 years with moderate to severe plaque psoriasis is supported by evidence from an open-label, single-arm, efficacy, safety and pharmacokinetics study (Ps STUDY 4) in 44 subjects. The safety and effectiveness of ustekinumab (Stelara) for pediatric patients less than 6 years of age have not been established.

The safety and effectiveness of ustekinumab (Stelara) have been established for treatment of psoriatic arthritis in pediatric individuals 6 to 17 years old. The safety and effectiveness of ustekinumab (Stelara) have not been established in pediatric patients less than 6 years old with psoriatic arthritis.

Description

CROHN'S DISEASE AND ULCERATIVE COLITIS

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology. IBD has two major categories: ulcerative colitis (UC) and Crohn's disease (CD). The most common symptoms in UC and CD are diarrhea, rectal bleeding, urgency to have bowel movements, abdominal cramps, pain, fever, and weight loss. Even though UC and CD have similar clinical presentations, they differ in the body areas affected. UC primarily causes inflammation of the mucosal lining and is generally limited to the colon and rectum, whereas CD affects the entire digestive system and can produce ulcers that extend deep into the intestinal wall.

The treatment of CD and UC is focused on stopping the inflammation and preventing flare-ups. The type of treatment depends on the type and severity of symptoms. Mild symptoms may respond to an antidiarrheal medicine such as

loperamide (e.g., Imodium). Treatment for individuals who may be having mild to moderate symptoms include aminosalicylates (and antibiotics for CD), whereas individuals with severe symptoms may be treated with corticosteroids, immunomodulators, or biologics.

PLAQUE PSORIASIS

Psoriasis is a chronic, immune-related disease of the skin that primarily affects adults. Plaque psoriasis is the most common form, characterized by scaling and inflammation. People with psoriasis may experience pain and itching, restricted motion in their joints, and emotional distress. Disease severity and clinical response to biologics may be measured with either the Psoriasis Area and Severity Index (PASI) or the Physician Global Assessment (PGA) scale.

The treatment of psoriasis consists of controlling inflammation and preventing discomfort through methods such as light therapy, stress reduction, and medications that suppress the immune response (e.g., topical corticosteroids or nonsteroidals, oral methotrexate, retinoids, cyclosporine).

PSORIATIC ARTHRITIS

It is estimated that up to 30% of individuals with psoriasis will also have (or will later develop) psoriatic arthritis. Psoriatic arthritis is another inflammatory disease characterized by psoriasis and episodes of joint pain and stiffness, which can lead to joint damage and progression of the number of joints involved. Disease severity and clinical response to biologics may be measured by the American College of Rheumatology (ACR) 20 response, defined as 20% improvement in tender and swollen joint counts and 20% improvement in at least three of the following five ACR core data set measures: pain, patient and physician global assessments, self-assessed physical disability, and acute phase reactant.

The treatment of psoriatic arthritis consists of controlling inflammation and preventing discomfort and joint damage. In addition to the treatment of the psoriasis, therapies such as exercise, physical or occupational therapy, and disease-modifying antirheumatic drugs (DMARDs) (e.g., sulfasalazine, azathioprine, hydroxychloroquine, cyclosporine, methotrexate, anti-tumor necrosis factor agents) may be initiated.

US FOOD AND DRUG ADMINISTRATION (FDA) APPROVAL OF USTEKINUMAB (STELARA)

Ustekinumab (Stelara) for subcutaneous injection received US Food and Drug Administration (FDA) approval on September 25, 2009 for the treatment of adult individuals (18 years or older) with moderate-to-severe plaque psoriasis and who are candidates for phototherapy or systemic therapy. This indication was later expanded to include pediatric individuals 6-17 years of age with moderate-to-severe plaque psoriasis and who are candidates for phototherapy or systemic therapy. In September 2013, the FDA approved ustekinumab (Stelara) for subcutaneous injection for the treatment of adult individuals (18 years or older) with active psoriatic arthritis, to be used alone or in combination with methotrexate; this indication was expanded in July 2022 to include pediatric individuals 6-17 years of age with active psoriatic arthritis. In September 2016, the FDA approved ustekinumab (Stelara) for intravenous infusion for the treatment of moderately to severely active Crohn's disease in adult individuals (18 years or older) who have failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed treatment with a tumor necrosis factor (TNF) blocker, or who failed or were intolerant to treatment with one or more TNF blockers. Subsequent maintenance therapy for Crohn's disease is by subcutaneous injection. In October 2019, the FDA approved ustekinumab (Stelara) for intravenous infusion and subsequent and subcutaneous injection for the treatment of adult individuals (18 years or older) with moderately to severely active ulcerative colitis who have failed or were intolerant to treatment with a biologic, corticosteroids, or immunomodulators.

Ustekinumab (Stelara) is a human IgG1κ monoclonal antibody (a human interleukin-12 and -23 antagonist) that binds with high affinity and specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses. In in vitro models, ustekinumab (Stelara) was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades.

PEER-REVIEWED LITERATURE

SUMMARY FOR PLAQUE PSORIASIS
Adults

FDA approval was based on two multicenter, randomized, double-blind, placebo-controlled studies (STUDY 1 and STUDY 2) that enrolled a total of 1,996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10 percent, a PASI score greater than 12, and who were candidates for

phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

STUDY 1 enrolled 766 subjects, and STUDY 2 enrolled 1,230 subjects. In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 40 percent to 44 percent of subjects in the studies. Approximately two-thirds of all subjects had received prior phototherapy. Sixty-nine percent of the subjects had received either prior conventional systemic therapy (56 percent) or biologic therapy (43 percent) for the treatment of psoriasis. A total of 28 percent of study subjects had a history of psoriatic arthritis.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75 percent reduction in PASI score (PASI 75) from baseline to week 12 and treatment success (cleared or minimal) on the PGA.

The studies had the same design through week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of ustekinumab (Stelara). Subjects randomized to ustekinumab (Stelara) received 45 mg or 90 mg doses, regardless of weight, at weeks 0, 4, and 16. Subjects randomized to receive placebo at weeks 0 and 4 crossed over to receive ustekinumab (Stelara) at weeks 12 and 16.

The clinical outcomes from both STUDY 1 and STUDY 2 at 12 weeks demonstrated a PASI 75 response of 3 percent to 4 percent in the placebo group, 66 percent to 76 percent response in the groups that received ustekinumab (Stelara) (45 mg or 90 mg). A PGA of cleared or minimal was demonstrated in 4 percent of the placebo group and in 59 percent to 73 percent in the groups that received ustekinumab (Stelara) (45 mg or 90 mg). In subjects who weighed less than 100 kg, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing.

Subjects in STUDY 1 were evaluated through week 52. At week 40, those who were PASI 75 responders at both weeks 28 and 40 (N=321) were re-randomized to either continued dosing of ustekinumab (Stelara) or to withdrawal of therapy (placebo) at week 40. At week 52, 89 percent (144/162) of subjects re-randomized to ustekinumab (Stelara) treatment were PASI 75 responders compared with 63 percent (100/159) of subjects re-randomized to placebo (treatment withdrawal after week 28 dose).

Adolescents 12-17 Years of Age

The safety and effectiveness of ustekinumab (Stelara) were studied in a multicenter, randomized, double-blind placebo-controlled trial (Ps STUDY 3) of 110 individuals ages 12 to 17 years who had a minimum body surface area involvement of 10 percent, a PASI score greater than 12, a PGA score greater than or equal to 3, were candidates for phototherapy or systemic therapy, and who were inadequately controlled by topical therapy. Participants were randomized (1:1:1) to receive placebo, ustekinumab (Stelara) recommended dose, or ustekinumab (Stelara) one-half of recommended dose at Weeks 0, 4, then every 12 weeks thereafter. At Week 12, the placebo group participants were crossed over to receive ustekinumab (Stelara) at either the recommended dose or one-half the recommended dose.

At Week 12, those who received ustekinumab (Stelara) had statistically significant greater outcomes compared to those on placebo: PGA score of cleared (0) or minimal (1) (69% ustekinumab [Stelara], 5% placebo), PASI 75 (80% ustekinumab [Stelara], 11% placebo), and PASI 90 (61% ustekinumab [Stelara], 5% placebo).

Individuals were followed for up to 60 weeks following first administration of study agent.

Children 6-11 Years of Age

The safety, effectiveness, and pharmacokinetics of ustekinumab (Stelara) were studied in an open-label, single-arm trial, multicenter, Phase 3 study (Ps STUDY 4; CADMUS Junior) of 44 individuals ages 6 to 11 years who had moderate to severe plaque psoriasis, defined by a minimum body surface area involvement of 10 percent, a PASI score greater than 12, a PGA score greater than or equal to 3, were candidates for phototherapy or systemic therapy, and who were inadequately controlled by topical therapy. Participants received ustekinumab (Stelara) at adolescent-recommended weight-based doses at Weeks 0, 4, then every 12 weeks thereafter through Week 40. The primary endpoint, the proportion of participants with a PGA score of cleared (0) or minimal (1) at week 12, was met by 77% of participants. Secondary endpoint outcomes included 84% of participants achieving PASI 75 and 64% achieving PASI 90 response.

SUMMARY FOR PSORIATIC ARTHRITIS

Adults

The FDA approval was based on two multicenter, randomized, double-blind, placebo-controlled studies (PsA STUDY 1, PsA STUDY 2) that enrolled a total of 927 individuals ages 18 years and older who had active psoriatic arthritis (defined as 5 or more swollen joints and 5 or more tender joints), despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or disease modifying antirheumatic drugs (DMARDs). The primary endpoint of the studies were ACR 20 response at Week 24.

The studies had the same design through week 24. In both studies, subjects were randomized to placebo, 45 mg or 90 mg of ustekinumab (Stelara) at weeks 0, 4, then every 12 weeks. At Week 16, individuals in the placebo group with less than 5% improvement in both tender and swollen joints were given ustekinumab (Stelara) 45 mg; individuals originally given ustekinumab (Stelara) 45 mg who had less than 5% improvement in both tender and swollen joints were given ustekinumab (Stelara) 90 mg. At Week 24, individuals remaining in the placebo group received ustekinumab (Stelara) 45 mg, which they continued at Week 28, then every 12 weeks thereafter.

Both studies showed a statistically significant greater proportion of individuals achieving ACR 20, ACR 50, and PASI 75 response in the ustekinumab (Stelara) 45 mg and 90 mg groups compared to placebo at Week 24. ACR 70 responses were also higher in the ustekinumab (Stelara) 45 mg and 90 mg groups, although the differences were not statistically significant. There was also a greater improvement in the secondary outcomes, such as enthesitis (inflammation at the site of tendon insertion into bone [e.g., Achilles tendon, planter fascia]) and dactylitis (inflammation of entire finger or toe). In addition, greater improvement in physical function (measured by the Health Assessment Questionnaire Disability Index [HAQ-DI]), was shown in the ustekinumab (Stelara) 45 mg and 90 mg groups compared to placebo at Week 24.

There were no significant differences in adverse events (including infections and serious adverse events) among all three groups (ustekinumab [Stelara] 45 mg and 90 mg groups and placebo group) at Week 16.

In the PsA STUDY 1, the follow-up period was continued through Week 52, where ACR 20 responses were still maintained.

Children 6-17 Years of Age

The safety, effectiveness, and pharmacokinetics of ustekinumab (Stelara) in children ages 6-17 years was supported by evidence from adequate and well controlled studies of ustekinumab (Stelara) in the following scenarios: adults with psoriasis and psoriatic arthritis (PsA), pharmacokinetic data from adults with psoriasis, adults with PsA and pediatric individuals with psoriasis, and safety data from two clinical studies in 44 pediatric individuals 6 to 11 years old with psoriasis, and 110 pediatric individuals 12 to 17 years old with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult individuals with psoriasis, adult individuals with PsA and pediatric individuals with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric individuals with PsA.

SUMMARY FOR CROHN'S DISEASE

The FDA approval was based on three randomized, double-blind, placebo-controlled clinical studies in adult individuals with moderately to severely active Crohn’s disease (Crohn’s Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy.

In studies CD-1 and CD-2, 1409 individuals were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, individuals were randomized to receive a single intravenous administration of ustekinumab (Stelara) at either approximately 6 mg/kg, placebo, or 130 mg (a lower dose than recommended).

In Study CD-1, individuals had failed or were intolerant to prior treatment with a tumor necrosis factor (TNF) blocker: 29% of individuals had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these individuals, 48% failed or were intolerant to one TNF blocker and 52% had failed two or three prior TNF blockers. At baseline and

throughout the study, approximately 46% of the individuals were receiving corticosteroids and 31% of the individuals were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the ustekinumab (Stelara) approximately 6 mg/kg group and 313 in the placebo group.

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

The maintenance study (CD-3), evaluated 388 individuals who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with ustekinumab (Stelara) in studies CD-1 or CD-2. Individuals were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab (Stelara) every 8 weeks or placebo for 44 weeks. At Week 44, 47% of individuals who received ustekinumab (Stelara) were corticosteroid-free and in clinical remission, compared to 30% of individuals in the placebo group. At Week 0 of Study CD-3, 34/56 (61%) ustekinumab (Stelara) treated individuals who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these individuals were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) individuals were in clinical remission at Week 0 while 16/61 (26%) of these individuals were in remission at Week 44. At Week 0 of Study CD-3, 46/72 (64%) ustekinumab (Stelara) treated individuals who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these individuals were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these individuals were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these individuals who were also naïve to TNF blockers, 34/52 (65%) of ustekinumab (Stelara) treated individuals were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm. Individuals who were not in clinical response 8 weeks after ustekinumab (Stelara) induction were not included in the primary efficacy analyses for study CD-3; however, these individuals were eligible to receive a 90 mg subcutaneous injection of ustekinumab (Stelara) upon entry into study CD-3. Of these individuals, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

SUMMARY FOR ULCERATIVE COLITIS
The FDA approval was based on two randomized, double-blind, placebo-controlled clinical studies in 961 adult individuals with moderately to severely ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, or immunomodulators (e.g., 6-MP or AZA therapy). Participants in received an intravenous induction dose of ustekinumab, either 130 mg (N= 320) or a weight-range-based dose that approximated 6 mg/kg of body weight (N=322) or placebo (N=319), and were reassed at Week 8. Those who responded were randomly assigned again to receive subcutaneous maintenance injections of 90 mg of ustekinumab either every 12 weeks (N=172) or every 8 weeks (N=176) or placebo (N=175).

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 subscore >1 [range, 0 to 3] on any of the four Mayo scale components). Week 8 results showed those who received ustekinumab (either 130 mg or 6 mg/kg dose) had higher rates of clinical remission compared to placebo (15.6%, 15.5%, vs 5.3%, respectively) (P<0.001 for both). Week 44 results showed those who received ustekinumab (either every 12 weeks or every 8 weeks) had higher rates of clinical remission compared to placebo (38.4%, 43.8%, vs 24%, respectively) (P = 0.002 and P<0.001, respectively). The rates of serious adverse events in those who received ustekinumab compared with placebo were similar.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

USTEKINUMAB (STELARA) FOR INTRAVENOUS INFUSION IS MEDICALLY NECESSARY WHEN REPORTED WITH THE FOLLOWING DIAGNOSIS CODES:

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
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
K51.40 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
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
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
K52.1 Toxic gastroenteritis and colitis

USTEKINUMAB (STELARA) FOR SUBCUTANEOUS INJECTION IS MEDICALLY NECESSARY WHEN REPORTED WITH THE FOLLOWING DIAGNOSIS CODES:
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
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

K51.40 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
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
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
K52.1 Toxic gastroenteritis and colitis
L40.0 Psoriasis vulgaris
L40.50 Arthropathic psoriasis, unspecified
L40.51 Distal interphalangeal psoriatic arthropathy
L40.52 Psoriatic arthritis mutilans
L40.53 Psoriatic spondylitis
L40.59 Other psoriatic arthropathy
L40.9 Psoriasis, unspecified

HCPCS Level II Code Number(s)

J3357 Ustekinumab, for subcutaneous injection, 1 mg

J3358 Ustekinumab, for intravenous injection, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From 08.00.82n:

10/24/2022	This version of the policy will become effective 10/24/2022. This policy was updated to communicate the medically necessary coverage position of pediatric individuals ages 6-17 years with active psoriatic arthritis, in alignment with

	the US Food and Drug administration (FDA) labeling. The following ICD-10 CM code has been removed from this policy, under the Heading of: USTEKINUMAB (STELARA) FOR INTRAVENOUS INFUSION AND SUBCUTANEOUS INJECTION R19.7 Diarrhea, unspecified

Revisions From 08.00.82m:

05/09/2022	This version of the policy will become effective 05/09/2022. This policy was updated to communicate the coverage criteria for the management of immunotherapy-related toxicities (diarrhea, colitits), in alignment with the National Comprehensive Cancer Network (NCCN) compendium. Continuation Therapy section has been updated as follows: **FROM:** Continuation therapy is considered medically necessary and, therefore, covered only for individuals whose previous course of treatment with ustekinumab (Stelara) resulted in documented improvement of symptoms or functions of affected areas. **TO:** Continuation therapy is considered medically necessary and, therefore, covered when the individual has met the coverage criteria for Initial Therapy, and the treatment with ustekinumab (Stelara) resulted in documented improvement of symptoms or functions of affected areas. The following ICD-10 CM codes have been **added** to this policy, under the Heading of: **USTEKINUMAB (STELARA) FOR INTRAVENOUS INFUSION AND SUBCUTANEOUS INJECTION** K52.1 Toxic gastroenteritis and colitis R19.7 Diarrhea, unspecified The following ICD-10 CM code has been **added** to this policy, under the Heading of: **USTEKINUMAB (STELARA) FOR SUBCUTANEOUS INJECTION** L40.9 Psoriasis, unspecified The following ICD-10 CM codes have been **revised** in this policy, to include a 3rd decimal digit: K50.01**3** Crohn's disease of small intestine with fistula K50.81**9** Crohn's disease of both small and large intestine with unspecified complications K50.91**3** Crohn's disease, unspecified, with fistula K51.31**1** Ulcerative (chronic) rectosigmoiditis with rectal bleeding K51.41**4** Inflammatory polyps of colon with abscess

Revisions From 08.00.82l:

08/11/2021	**The policy has been reviewed and reissued to communicate the Company's continuing position on ustekinumab (Stelara®).**
10/12/2020	This version of the policy will become effective 10/12/2020. This policy was updated to communicate the coverage criteria changes for the expanded FDA approval of ustekinumab (Stelara®) for the treatment of plaque psoriasis to include individuals 6-11 years of age.

Revisions From 08.00.82k:

01/06/2020	This version of the policy will become effective 01/06/2020. This policy was updated to communicate the coverage criteria for the new

	FDA approval of ustekinumab (Stelara®) for the treatment of ulcerative colitis, including dosing and frequency requirements. Prior medications used in Crohn's disease have also been updated.

Revisions From 08.00.82j:

09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
11/21/2018	This policy has been reissued in accordance with the Company's annual review process.
01/01/2018	This policy has been identified for the HCPCS code update, effective 01/01/2018. The following HCPCS code has been **added** to this policy: J3358 Ustekinumab, for intravenous injection, 1 mg The following HCPCS code has been **removed** from this policy: Q9989 Ustekinumab, for Intravenous Injection, 1 mg

Revisions From 08.00.82i:

11/01/2017	This policy was updated to: • Communicate the new FDA approval for use in adolescents with moderate to severe plaque psoriasis. • Clarify The Company's Dosing and Frequency Requirements for ustekinumab (Stelara®) and the removal of the Risk Evaluation and Mitigation Strategy (REMS) program by the US Food and Drug Administration.

Effective 10/05/2017 this policy has been updated to the new policy template format.
Version Effective Date:
10/24/2022
Version Issued Date:
10/24/2022
Version Reissued Date:
N/A