MEDICAL POLICY

POLICY TITLE	USTEKINUMAB (STELARA®)
POLICY NUMBER	MP-2.140

Original Issue Date (Created):	**January 1, 2010**
Most Recent Review Date (Revised):	**January 28, 2014**
Effective Date:	**April 1, 2014**

I. POLICY

Preauthorization Requirements for Ustekinumab (STELARA®)

Note: Request for **Ustekinumab (STELARA®)** must be accompanied by a completed preauthorization form prior to treatment, at 12 weeks and then every 12 months during treatment. Various index tools have been developed to assess the severity and monitor the efficacy of treatment for the conditions as addressed in this policy, and any appropriate index form may be used providing improvement can be measured.

Note: Patients **must** be tested for latent tuberculosis prior to receiving Ustekinumab (STELARA®); if positive, treatment for TB should be started prior to starting (STELARA®).

Adult Use: Ustekinumab (STELARA®) is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and for active, psoriatic arthritis alone or in combination with methotrexate.

Pediatric Use: Safety and effectiveness of Ustekinumab (STELARA®) in pediatric patients have not been evaluated.

Note: Initial Authorization: If the patient has been maintained on successful treatment with Ustekinumab (Stelara) for at least six months prior to this initial authorization with Capital Blue Cross, Ustekinumab (Stelara) may be considered medically necessary.

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Ustekinumab (STELARA®), a human interleukin-12 and -23 antagonist is considered **medically necessary** for the treatment of adult patients (18 years or older) with the following conditions:

- **moderate to severe plaque psoriasis (Ps)** who are candidates for phototherapy or systemic therapy; or
- **active psoriatic arthritis (PsA)**, alone or in combination with methotrexate.

Initial Therapy moderate to severe plaque psoriais:

- Consulting Dermatologist recommends treatment with Ustekinumab (STELARA®) **AND**
- The patient has not responded to or has a contraindication to non-biologic DMARDS; (e.g., Methotrexate, Azathioprine, Cyclosporine); **AND**
- The patient has not responded to or has a contraindication to phototherapy; (e.g., ultraviolet B (UVB) or oral methoxsalen plus UVA light (PUVA) for psoriasis.

Initial Therapy active psoriatic arthritis

- Consulting Dermatologist recommends treatment with Ustekinumab (STELARA®) **AND**
- The patient has not responded to or has a contraindication to non-biologic DMARDS; (e.g., Methotrexate, Azathioprine, Cyclosporine); **AND**
- The patient may take ustekinumab (Stelara) alone or in combination with methotrexate.

Maintenance Therapy:

- Ustekinumab (STELARA®) maintenance therapy may be considered **medically necessary** when therapy has demonstrated efficacy as evidence by an improvement in the tool at 12 weeks and maintenance of at least that improvement at each twelve month re-evaluation.

***As measured by a standardized disease activity tool (e.g. Simplified Psoriasis Area Severity Index (SPASI), Psoriasis Area Severity Index (PASI).*

Ustekinumab (STELARA®) as a biological treatment of psoriasis for indications other than those addressed in the policy is considered **not medically necessary**.

Cross-reference:

MP-2.046 Ultraviolet Light Therapies
MP-2.103 Off-Label Use of Prescription Drugs
MP-2.176 Self-Administered Medications

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II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N]Capital Cares 4 Kids
[N] PPO
[N] HMO
[Y] SeniorBlue HMO* (also see note)
[Y] SeniorBlue PPO* (also see note)
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO**

*Step therapy requiring a trial of self-administered biologic therapy or similar self administered injectable or oral medication does not apply

*Note: "FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if determined that the use is medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice." Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug)." *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*

** The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

III. DESCRIPTION/BACKGROUND

Plaque Psoriasis

Plaque psoriasis, the most common form of psoriasis, is a chronic relapsing disease of the skin characterized by scaling and inflammation. Psoriasis is an autoimmune disease in which skin cells multiply ten (10) times faster than the normal rate, causing excess cells to pile on the surface of the skin resulting in raised scaly patches that can be very disfiguring. Symptoms of psoriasis include pain, itching, restricted joint motion, and emotional distress. Mild psoriasis can be controlled with topical medications whereas moderate to severe psoriasis requires ultraviolet or systemic therapies. Narrow band ultraviolet light therapy B (NB-UVB) is noted to be more effective than broadband UVB.

Psoriatic Arthritis

Psoriatic arthritis is joint inflammation that is associated with psoriasis. Psoriatic arthritis is a potentially destructive and deforming form of arthritis that affects approximately 10 percent of persons with psoriasis. Joint pain, stiffness and swelling are the main symptoms of psoriatic

arthritis. Generally, the treatment of arthritis in psoriatic arthritis involves a combination of anti-inflammatory medications (NSAIDs) and exercise. If progressive inflammation and joint destruction occur despite NSAIDs treatment, more potent medications such as methotrexate (Rheumatrex, Trexall), corticosteroids, and antimalarial medications (such as hydroxychloroquine, or Plaquenil) are used.

Ustekinumab (STELARA®)

Ustekinumab (STELARA®) is a human monoclonal antibody 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 cytokines contribute to the overproduction of skin cells and inflammation associated with psoriasis. Stelara targets these 2 cytokines. The clinical significance of these characteristics is not fully known. It is indicated for the treatment of moderate to severe plaque psoriasis in adults, who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills). The effectiveness and safety of Stelara for plaque psoriasis was evaluated in 3 studies that involved more than 2,200 patients.

Centocor first applied for approval of Stelara in December 2007 and an advisory committee recommended approval in June 2008. The FDA extended the review due to concerns about cancer and infection risks -- but has granted approval now with strategies for communication about risk, including a medication guide for patients.

In September of 2013, The FDA approved ustekinumab (Stelara) for the treatment moderate-to-severe psoriatic arthritis in adult patients. The approval was based on the findings of two phase III studies of this fully human monoclonal antibody, which targets two cytokines, interleukin (IL)-12 and IL-23.

Ustekinumab (STELARA®) General Administration Information

STELARA® is for subcutaneous administration. STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. After proper training in subcutaneous injection technique, a patient may self-inject with STELARA® if a physician determines that it is appropriate. Frequency of monitoring should be decided on an individual basis, depending on symptoms, severity and drug treatment.

According to the FDA, the recommended doses are as follows:

Psoriasis

- For patients weighing less than or equal to100 kg is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. The recommended dose for patients weighing greater than 100 kg is 90 mg initially and 4 weeks later, followed by 90mg every 12 weeks.

Psoriatic Arthritis

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

IV. RATIONALE

Two multicenter, randomized, double-blind, placebo-controlled studies (STUDY 1 and STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score >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 1230 subjects. 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 STELARA®. Subjects randomized to 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 STELARA® (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

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 44% of subjects in STUDY 1 and 40% of subjects in STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of study subjects had a history of psoriatic arthritis.

Clinical Response

The results of STUDY 1 and STUDY 2 are presented in Table 3 below.

Table 3. Clinical Outcomes STUDY 1 and STUDY 2

Week 12	STUDY 1			STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to STELARA® among these subgroups.

In subjects who weighed <100 kg, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed >100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 4 below).

Table 4. Clinical Outcomes by Weight STUDY 1 and STUDY 2

	STUDY 1			STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
PASI 75 response at Week 12*	4%	74%	65%	4%	73%	78%
≤ 100 kg	6/166	124/168	107/164	12/290	218/297	225/289
>100 kg	2% 2/89	54% 47/87	68% 63/92	3% 3/120	49% 55/112	71% 86/121

PGA of Cleared or Minimal at Week 12*	4%	64%	63%	5%	74%	75%
≤ 100 kg	7/166	108/168	103/164	14/290	220/297	216/289
>100 kg	3%	49%	58%	3%	51%	69%
	3/89	43/87	53/92	4/120	57/112	84/121

*Patients were dosed with study medication at Weeks 0 and 4.

Subjects in STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

Psoriatic Arthritis

The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with an anti-TNFα agent, of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Clinical Response

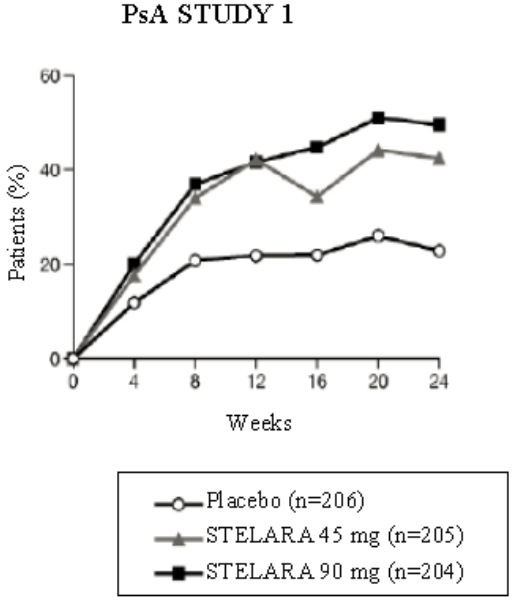
In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 4). ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups,

Table 1: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

	PsA STUDY 1			PsA STUDY 2		
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Number of patients randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with ≥ 3% BSA[a]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

Figure 1: Percent of patients achieving ACR 20 response through Week 24



The results of the components of the ACR response criteria are shown in Table 5.

Table 5: Mean change from baseline in ACR components at Week 24			
	PsA STUDY 1		
		STELARA®	
	Placebo (N=206)	45 mg (N= 205)	90 mg (N= 204)
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints [b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)
[b] Number of tender joints counted (0-68)
[c] Visual analogue scale; 0= best, 10=worst.
[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
[e] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at Week 24.

Physical Function

STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24.

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V. DEFINITIONS

IL-12 AND IL23- Interleukins, like other cytokines, are often involved in stimulating or suppressing the immune system and inflammation (as is the case with their role in psoriasis). Interleukins are typically referred to by number, for example: IL-1, IL-2, etc. Recent studies have shown that IL-12 and IL-23 are very important in the development of psoriasis. The two are closely related and share a significant portion of their design; in fact, recent biologic drugs for psoriasis treatment have been developed to block IL-12/IL-23 simultaneously.

MONOCLONAL ANTIBODIES- Antibodies are proteins that are generated by the immune system, specifically the white blood cells. They circulate in the blood and attach to foreign proteins called antigens in order to destroy or neutralize them. For example, when you are exposed to a virus, your body will produce antibodies to help rid your system of the infection. Monoclonal antibodies are laboratory produced substances that can locate and bind to specific molecules such as tumor necrosis factor (TNF).

TUMOR NECROSIS FACTOR (TNF) is a natural body protein, also produced synthetically, with anticancer effects. The body produces it in response to the presence of toxic substances such as bacterial toxins.

MODERATE PSORIASIS-psoriasis affecting 3-10% of the body.

PSORIASIS AREA SEVERITY INDEX (PASI) is a tool used for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease). The body is divided into four sections (head (10% of a person's skin); arms (20%); trunk (30%); legs (40%). Each of these areas is scored by itself, and then the four scores are combined into the final PASI. For each section, the percent of area of skin involved, is estimated and then transformed into a grade FROM) 0 to 6.Severe Psoriasis-psoriasis affecting greater than 10% of the body.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual Publication 100-02. Chapter 15 Section 50.4.2 Unlabeled Use of Drug Effective 10/01/03. [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf . Accessed November 1, 2013.

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual Publication 100-02 Chapter 15 Sections 50, 50.4.1, 50.4.3 Drugs and Biologicals Effective 10/01/03 [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf . Accessed. November 1, 2013.

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National Institute for Health and Clinical Excellence (NICE) Ustekinumab for the treatment of adults with moderate to severe psoriasis London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Sep. 31 p. (Technology appraisal guidance; no. 180) [Website] : http://www.guideline.gov. Accessed November 1, 2013.

Smith CH, A.V. Anstey, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. London, UK: BAD. [Website]: http://www.guideline.gov. Accessed November 1, 2013.Stelara prescribing information September 2013. Stelara [Website]:http://www.stelarainfo.com. Accessed November 1, 2013.

U.S. Food and Drug Administration FDA Approves first Biologic Therapy for Psoriasis [Website]: http://www.fda.gov. Accessed November 1, 2013.

IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

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Covered when medically necessary:

HCPCS Code	Description
J3357	INJECTION, USTEKINUMAB, 1MG

ICD-9-CM Diagnosis Code*	Description
696.0	PSORIATIC ARTHROPATHY
696.1	OTHER PSORIASIS
696.2	PARAPSORIASIS

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

X. POLICY HISTORY

MP-2.140	**CAC 11/24/09** new policy.
	Admin Change 8/3/11 Preauthorization requirements changed from prior to treatment, at 4 weeks, at 12 weeks and every 3 months during treatment to prior to treatment, at 12 weeks and every 6 months during treatment. Added "or has contraindications to" the second and third bullet under initial therapy. Changed three-month re-evaluation to six-month re-evaluation under Maintenance Therapy.
	Admin Change 9/12/2011 Removed AND from page 2: Initial Therapy to correct criteria bullet.
	CAC 4/24/12 Consensus, no changes, references updated**.**
	CAC 6/4/13 Preauthorization requirements changed from prior to treatment, at 12 weeks and every 6 months during treatment to prior to treatment, at 12 weeks and every 12 months during treatment. No changes to other policy statements.
	Administrative change 8/21/13 Updated administration information. A patient may self-inject with STELARA if a physician determines that it is appropriate. Added Medicare variation "Step therapy requiring a trial of self-administered biologic therapy or similar self administered injectable or oral medication does not apply". Added rationale section.
	CAC 1/28/14 Minor revision. Policy being revised to add new FDA approved indication for active psoriatic arthritis alone or in combination with methotrexate. References, rationale, and background updated.

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