PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sylvant Prior Authorization Policy
- Sylvant® (siltuximab intravenous infusion – EUSA Pharma)

REVIEW DATE: 01/18/2023

OVERVIEW

Sylvant, an interleukin (IL)-6 antagonist, is indicated for treatment of patients with **multicentric Castleman's disease** (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.[1] Because Sylvant did not bind to virally produced IL-6 in a nonclinical study, Sylvant has not been studied in patients with MCD who are HIV positive or HHV-8 positive. The pivotal trials showed a higher proportion of patients with durable tumor response (partial or complete response) and improvement in patient-reported outcomes (e.g., fatigue, physical function) with Sylvant vs. placebo. Patients were treated until treatment failure, defined as disease progression based on increased symptoms, radiologic progression, or deterioration in performance status. Safety and efficacy has not been established in patients < 18 years of age.

Disease Overview

MCD affects approximately 1,000 patients in the US. It typically presents with lymphoid hyperplasia at multiple sites, including the peripheral lymph nodes, bone marrow, and multiple organs. Patients often have serious infections, fevers, weight loss, fatigue, night sweats, and nerve damage that can cause weakness and numbness. Persistent IL-6 production has been implicated in the development of various autoimmune, chronic, inflammatory diseases and cancers, including MCD.[2] Sylvant, a human-mouse chimeric monoclonal antibody that is produced by Chinese hamster ovary cells, binds human IL-6 and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 5.2022 – July 12, 2022) list Sylvant as a treatment option for MCD and for refractory or relapsed unicentric disease.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sylvant. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sylvant as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Sylvant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Sylvant for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sylvant is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Castleman's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has multicentric Castleman's disease; OR
       - **b)** Sylvant is being used for relapsed or refractory unicentric Castleman's disease; AND
     - **iv.** Sylvant is prescribed by or in consultation with an oncologist or hematologist.
   - **B)** Patient is Currently Receiving Sylvant. Approve for 1 year if the patient meets both of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least ONE of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate, fibrinogen, albumin, and/or hemoglobin), increased body mass index, and/or reduction in lymphadenopathy.
       - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement or resolution of constitutional symptoms (e.g., fatigue, physical function).

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Sylvant is not recommended in the following situations:

1. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

2. **Multiple Myeloma**. Efficacy is not established. In a Phase II study (n = 286) evaluating patients with relapsed or refractory multiple myeloma, median progression-free survival was similar in patients treated with Velcade (bortezomib injection) + Sylvant (8.0 months) vs. in those treated with Velcade + placebo (7.6 months).[4] Following 24.5 months of follow-up, there was not a significant difference between the groups in median overall survival (30.8 months in the group that received Velcade + Sylvant vs. 36.8 months in the Velcade + placebo group). There was not a significant difference in overall response rate or other secondary endpoints. Another Phase II study evaluated Sylvant in patients (n = 106) with previously untreated symptomatic multiple myeloma who were transplant-ineligible.[6] There was not a significant difference in complete response rate or overall response rate in patients treated with Velcade/melphalan/prednisone (VMP) vs. those treated with VMP + Sylvant. Progression-free survival and overall survival was the same in the two treatment groups. Another Phase II study in

adults with relapsed or refractory multiple myeloma did not show any response with Sylvant monotherapy compared with 8% response rate in those who received Sylvant + dexamethasone.[7]

3. **Myelodysplastic Syndrome (MDS).** Efficacy is not established. A double-blind, placebo-controlled, Phase II study assigned adults with MDS (n = 76) to treatment with best supportive care in combination with Sylvant or placebo.[5] There was not a significant difference in the proportion of patients with reduced transfusions to treat anemia (primary endpoint). The study was terminated early due to lack of efficacy.

4. **Prostate Cancer.** Efficacy is not established. An open-label Phase II study did not demonstrate added efficacy with Sylvant added on to mitoxantrone/prednisone vs. mitoxantrone/prednisone.[8] Although the treatment groups were not balanced, progression-free survival was 97 days in the group that received Sylvant/mitoxantrone/prednisone vs. 228 days with mitoxantrone/prednisone. The study was stopped early.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Sylvant® intravenous infusion [prescribing information]. Hemel Hempstead, Hertfordshire, UK: EUSA Pharma; April 2022.
2. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. *Int J Biol Sci*. 2012;8(9):1227-1236.
3. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2022 – July 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 17, 2023.
4. Orlowski RZ, Gercheva L, Williams C, et al. A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. *Am J Hematol*. 2015;90(1):42-49.
5. Garcia-Manero G, Gartenberg G, Steensma DP, et al. A phase 2, randomized, double-blind, multicenter study comparing siltuximab plus best supportive care (BSC) with placebo plus BSC in anemic patients with International Prognostic Scoring System low- or intermediate-1-risk myelodysplastic syndrome. *Am J Hematol*. 2014;89(9):E156-62.
6. San-Miguel J, Bladé J, Shpilberg O, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. *Blood*. 2014;123(26):4136-4142.
7. Voorhees PM, Manges RF, Sonneveld P, et al. A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. *Br J Haematol*. 2013;161(3):357-366.
8. Fizazi K, De Bono JS, Flechon A, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. *Eur J Cancer*. 2012;48(1):85-93.