

POLICY: Oncology – Sylvant® (siltuximab intravenous infusion – EUSA Pharma)

DATE REVIEWED: 02/19/2020; selected revision 03/25/2020

OVERVIEW

Sylvant is an interleukin (IL)-6 antagonist 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 interleukin (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.

Dosing Information

Do not reduce the dose of Sylvant.¹ Laboratory monitoring is recommended during treatment. If parameters for absolute neutrophil count, platelet count, and/or hemoglobin are not met, consider delaying treatment.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 1.2020 – January 22, 2020) list Sylvant as a treatment option for MCD and for refractory or relapsed unicentric disease.³

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Sylvant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 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.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

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. The patient is an adult ≥ 18 years of age; AND
 - ii. The patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND
 - iii. The patient meets ONE of the following (a or b):
 - a) The 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 has responded to Sylvant, as determined by the prescriber.

Note: Examples of a response include stabilized disease; tumor response; and resolution or stabilization of symptoms, such as fatigue and physical function.

Dosing. Approve if the dose is 11 mg/kg as an IV infusion administered once every 3 weeks.¹

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sylvant has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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 on 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. 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[®] for intravenous injection [prescribing information]. Hemel Hempstead, Hertfordshire, UK: EUSA Pharma; December 2019.
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 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on February 12, 2020.
4. Orłowski 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.
9. Centers for Disease Control and Prevention (Web site). Coronavirus (COVID-19). Updated March 22, 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/index.html/>. Accessed on March 23, 2020.
10. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2020 Mar 23]. Available from: <https://clinicaltrials.gov/ct2/results?cond=Coronavirus&term=tocilizumab&cntry=&state=&city=&dist=>. Search terms: coronavirus, tocilizumab.
11. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Available at: [file:///C:/Users/MMedina/Downloads/202003.00026v1%20\(1\).pdf](file:///C:/Users/MMedina/Downloads/202003.00026v1%20(1).pdf). Accessed on March 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	08/01/2018
Early annual revision	--	02/20/2019
Annual revision	No changes to criteria.	02/19/2020
Selected revision	COVID-19: This indication (including use for cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	03/27/2020