

Siltuximab (Sylvant®)**Criteria for Use****April 2016**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria If the answer to ANY item below is met, then the patient should NOT receive siltuximab.

- Care for the disease being treated not provided by a VA or VA purchased care (e.g. Choice Program, Fee Basis) hematology/oncology provider.
- HIV (human immunodeficiency virus) positive and/or HHV-8 (human herpes virus) positive (see Issues for Consideration)
- Chronic or unresolved infection (see Issues for consideration)
- Hypersensitivity reaction to siltuximab or its inactive ingredients: L-histidine, polysorbate 80 and sucrose
- Severe hepatic impairment (Child-Pugh C). (see Issues for Consideration)
- Absolute Neutrophil Count (ANC) $< 1.0 \times 10^9$ /L prior to first dose (see Dosage and Administration for SUBSEQUENT doses)
- Platelet count $< 75 \times 10^9$ /L prior to first dose (see Dosage and Administration for SUBSEQUENT doses)
- Hemoglobin ≥ 17 g/dL prior to first dose (see Dosage and Administration for SUBSEQUENT doses)

Inclusion Criteria The following must be fulfilled in order to meet criteria.

- Diagnosis of Multicentric Castleman's Disease (MCD)

AND

- Goals of care and role of palliative care consult have been discussed and documented.
- ECOG* Performance Status 0 - 2

For women of childbearing potential

- Pregnancy should be excluded prior to receiving siltuximab and the patient provided contraceptive counseling on potential risk vs. benefit of taking siltuximab if patient were to become pregnant.
- Effective contraception should be utilized during and for 3 months after siltuximab treatment.

* ECOG Eastern Cooperative Oncology Group

Dosage and Administration

- Siltuximab dose is 11 mg/kg over 1 hour as an IV infusion every 3 weeks
- Discontinue in patients with severe infusion-related reactions, anaphylaxis, severe allergic reactions or cytokine release syndromes. Do not reinstitute treatment.
- Hematologic lab tests should be performed prior to each siltuximab dose for the first 12 months and every 3 dosing cycles thereafter. Refer to Table 1. Treatment Criteria. If criteria are not met, consider delaying treatment. Do not reduce dose.

Table 1. Treatment Criteria

Hematologic lab parameter	Criteria prior to FIRST dose	Criteria prior to SUBSEQUENT doses
ANC	$\geq 1.0 \times 10^9$ /L	$\geq 1.0 \times 10^9$ /L
Platelet count	$\geq 75 \times 10^9$ /L	$\geq 50 \times 10^9$ /L
Hemoglobin [#]	< 17 g/dL	< 17 g/dL

[#] Siltuximab may increase hemoglobin levels in MCD patients

Monitoring

- Patients with concurrent CYP450 substrate therapies with narrow therapeutic indices: Monitor for therapeutic effect (e.g. warfarin) or drug concentration (e.g. cyclosporine or theophylline) upon initiation or discontinuation of siltuximab and as needed and adjust dose. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after therapy is stopped. Exercise caution when siltuximab is co-administered with CYP3A4 substrate drugs (e.g. oral contraceptives, lovastatin, atorvastatin) as siltuximab may result in reduced efficacy of these agents.
- Resistance to infection may be lowered during siltuximab therapy. Inform patients to notify their provider immediately should signs/symptoms suggestive of infection develop.
- Signs/symptoms of allergic reactions during the infusion, which may include difficulty breathing, chest tightness, wheezing, severe dizziness or light-headedness, swelling of lips or skin rash.
- Signs/symptoms of infusion-related reactions, which may include back pain, chest pain or discomfort, nausea/vomiting, flushing, erythema and palpitations.
- Gastrointestinal (GI) perforation has been reported in clinical trials, but not in the MCD trials. Use cautiously in patients who may be at risk of GI perforation. Immediately evaluate any patient presenting with symptoms suggestive of GI perforation.
- Evidence of disease response or progression (via radiographic scan or symptomatology). Assess disease signs and symptoms prior to each cycle of siltuximab with disease status evaluation every 3 months.

Issues for Consideration

- Limitation of Use: Siltuximab was not studied in patients with MCD who are HIV positive or HHV-8 positive, as virally produced IL-6 was not shown to bind to siltuximab in a nonclinical study.
- Siltuximab may mask signs/symptoms of acute inflammation with its suppression of fever and acute phase reactants such as C-reactive protein. Therefore it should not be given to patients with severe infections.
- Live vaccines should not be administered during siltuximab therapy as IL-6 inhibition may interfere with the normal immune response.
- Pharmacokinetic analysis notes no significant difference in clearance in those with mild-moderate hepatic impairment (Child-Pugh Classes A and B). Patients with severe hepatic impairment (C-P Class C) were not included in clinical trials.

Discontinuation Recommendations

- Patient develops signs of anaphylaxis during the infusion
- Persistent, severe infusion-related reactions despite adequate premedication (e.g. antihistamines, acetaminophen and corticosteroids)
- Non-compliance with therapy, laboratory or follow-up requests
- Decline in ECOG performance status to level unacceptable for patient to maintain quality of life*
- Persistent or recurring toxicity despite a 3-week delay in dosing
- Evidence of progressive disease

*ECOG Performance Status *Am J Clin Oncol* 1982; 5: 649-655

0, fully active without restriction

1, restricted strenuous activity, but able to carry out light work

2, ambulatory/capable self-care, unable to carry out work activities

3, confined to bed/chair more than 50% of time

4, totally confined to bed/chair

5, dead

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Updated versions may be found at <http://www.pbm.va.gov> or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx>