

Siltuximab (Sylvant) National Drug Monograph January 2016

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

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Siltuximab is an interleukin-6 (IL-6) antagonist for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. Overproduction of IL-6 has been associated with systemic manifestations of MCD. Siltuximab binds to IL-6, thereby preventing binding to IL-6 receptors.
Indication(s) Under Review	Indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. Limitation of use: siltuximab was not studied in MCD patients who are HIV positive or HHV-8 positive because siltuximab did not bind to virally produced IL-6 in a nonclinical study
Dosage Form(s) Under Review	100 mg of lyophilized powder in a single-use vial 400 mg of lyophilized powder in a single-use vial
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS
Pregnancy Rating	Pregnancy Category C

Executive Summary

Efficacy	<ul style="list-style-type: none"> Siltuximab is the first FDA-approved treatment of MCD, which is considered a rare condition that has no treatment standard. No other drug has FDA-approval for the treatment of MCD. FDA-approval was based upon achievement of durable tumor and symptomatic response (defined as complete or partial response) sustained for 18 weeks. Compared to placebo, a significant difference ($p=0.0012$) was noted between the durable tumor and symptomatic responses in the siltuximab vs. placebo arms (34 vs. 0%, respectively). 								
Safety	<ul style="list-style-type: none"> Siltuximab is associated with Infusion-Related Reactions (IRR) and should therefore be administered in a setting appropriate to managing these reactions. As siltuximab may mask signs and symptoms of acute inflammation, patients with infection should not receive siltuximab until the infection resolves. Although not noted in MCD trials, siltuximab has been associated with GI perforation, so patients should be appropriately monitored for such. 								
Other Considerations	<table border="1" style="width: 100%;"> <tr> <td style="width: 40%;">Outcome in clinically significant area</td> <td>Durable tumor and symptomatic response, sustained for at least 18 weeks</td> </tr> <tr> <td>Effect Size</td> <td>Difference in outcomes between groups</td> </tr> <tr> <td>Potential Harms</td> <td>Grade 3 \geq toxicities: fatigue 9%, night sweats 8%, generalized edema 8%</td> </tr> <tr> <td>Net Clinical Benefit</td> <td>Substantial (high benefit with low risk of harm)</td> </tr> </table> <p>Definitions Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life</p>	Outcome in clinically significant area	Durable tumor and symptomatic response, sustained for at least 18 weeks	Effect Size	Difference in outcomes between groups	Potential Harms	Grade 3 \geq toxicities: fatigue 9%, night sweats 8%, generalized edema 8%	Net Clinical Benefit	Substantial (high benefit with low risk of harm)
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	<p>Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio</p> <p>Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)</p> <p>Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)</p>
Potential Impact	<ul style="list-style-type: none"> Siltuximab should be limited to MCD patients that are HIV-negative and HHV-8 negative as virally produced IL-6 was shown not to bind to siltuximab in a nonclinical study.

Background

Purpose for review

FDA approval 2014

Issues to be determined:

- ✓ Evidence of need
- ✓ Does siltuximab offer advantages to currently available alternatives?
- ✓ Does siltuximab offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does siltuximab have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Siltuximab is the first FDA-approved treatment for MCD.

LAD lymphadenopathy
HPV human papilloma virus
IRR infusion-related reactions
HIV human immunodeficiency virus
PML progressive multifocal leukoencephalopathy

Formulary Alternatives	Other Considerations
Rituximab (off label use)	Evidence to support use in HIV-associated MCD; Dosing not standard: 375 mg/m ² IV infusion every 28 days vs. every week x 4 doses; Risk of infusion-related reactions (IRR) Boxed warning for HPV reactivation, severe IRR, severe mucocutaneous reactions and PML
Non-formulary Alternative (if applicable)	Other Considerations
Tocilizumab (off label use)	Approved for use in Japan since 2005 based upon a single, nonrandomized study of 28 patients. LAD improved after 16 weeks of therapy; Dose 8 mg/kg IV infusion every 2 weeks; IRR 4-16% Boxed warning for risk of serious infection; Increased risk serum cholesterol, hepatotoxicity, bone marrow suppression

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms siltuximab and Sylvant. The search was limited to studies performed in humans and published in the English language. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

- Due to the rare nature of MCD, only one randomized trial has been performed.¹
- A randomized, placebo-controlled trial at 38 hospitals in 19 countries was performed in adult patients with confirmed diagnosis of MCD. Patients with measurable disease (not limited to cutaneous lesions), grade 1 or greater disease symptoms according to NCI-CTCAE version 4.0 and ECOG Performance Status score of 0-2 were included. Patients could be newly diagnosed or previously treated. Those receiving corticosteroids were placed on stable or decreasing doses of corticosteroids (no more than 1 mg/kg/day prednisone equivalent) 4 weeks prior to randomization. Excluded patients were those who were HIV seropositive, evidence of HHV-8, Hepatitis B or C infection or had a history of or concurrent lymphoma. Prior targeted IL-6 treatment was not permitted.
- Patients were randomized 2:1 to siltuximab or placebo every 3 weeks (one cycle). All patients received best supportive care (BSC), which included management of effusions, use of antipyretic, antipruritic,

antihistamine and pain drugs, management of infections, transfusions and standard management of infusion-related reactions.

- Siltuximab was discontinued at treatment failure, which was defined as sustained increase in grade ≥ 2 disease-related symptoms persisting ≥ 3 weeks; new disease-related grade ≥ 3 symptoms; sustained > 1 point increase in ECOG-PS persisting for ≥ 3 weeks; radiological progression or initiation of another treatment for MCD. Placebo was discontinued at first treatment failure, at which time patients could receive open-label siltuximab plus BSC.
- Primary endpoint was durable tumor and symptomatic response, defined as complete (CR) or partial response (PR) assessed by independent review per modified Cheson criteria.² Symptomatic response was defined as complete resolution or stabilization of 34 Castleman's disease-related symptoms as defined by the multicentric Castleman's disease-related overall symptom score, calculated as the sum of the NCI-CTCAE severity grades. At the start of each cycle, the percent change from baseline was calculated.
- Secondary endpoints included duration of tumor and symptomatic response, change in hemoglobin concentration, discontinuation of corticosteroids, treatment failure rate, disease-related symptoms, overall survival at 1 year and patient-reported outcomes.
- The study population (n=79; siltuximab n=53; placebo n=26) demographics were well-balanced except for male gender (57 vs. 85%, siltuximab vs. placebo, respectively). Median age was 48 years (range, 20-78). All patients had symptomatic disease and 78% had more than 3 symptoms. Most patients had received previous treatment (55 vs. 65%, respectively)
- During masked treatment, a median of 19 (range, 1-50) siltuximab and 8 (range 2-32) placebo cycles were completed. At least one dose delay was noted in 40% of those in the siltuximab arm.

Key Efficacy Endpoints

	Siltuximab (n=53)	Placebo (n=26)	Difference
Primary endpoints			
Durable tumor/symptomatic response	18 (34%)	0 (0%)	34% (95% CI, 11.1-54.8); p=0.0012
Complete response	1 (2%)	0 (0%)	
Partial response	17 (32%)	0 (0%)	
Duration of response	383 days (232-676)	-	
Secondary endpoints			
Time to tumor response	155 days (44-742)	65 days	
Durable symptomatic response rate	30 (57%)	5 (19%)	37.4% (95% CI, 14.9-58.2); p=0.0018
Complete symptom response	13 (25%)	0 (0%)	24.5% (95% CI, 1.4 - 46.2); p=0.0037
Time to durable symptom response	170 days (67-274)	NE (227-NE)	2.774 (95% CI, 1.068-7.206); p=0.0288
Time to treatment failure	NE (378-NE)	134 (85-NE)	0.418 (95% CI, 0.214-0.815); p=0.0084
Hgb conc \uparrow of ≥ 15 g/L at week 13	19 (61%)	0 (0%)	61.3% (95% CI, 28.3-85.1); p=0.0002
Patients who discontinued steroids	4 (31%)	1 (11%)	19.7% (95% CI, -23.6-56.7); p=0.3602

NE = not evaluable

- Evidence provided at the American Society of Hematology 2014 Annual Meeting indicated that siltuximab can improve patient-reported outcomes to a level of general population health norms. In the domains of Vitality OR 5.3 (p=0.049), Role-emotional OR 5.5 (p=0.011) and Social functioning OR 11.4 (p=0.014), the odds ratios are significant. A trend was noted in the Role-physical domain with OR 5.5 (p=0.067). These norms are based upon the US general population Short-Form-36.¹²

Potential Off-Label Use

Studies with siltuximab are ongoing although some reports to-date, have not been very promising.

According to www.clinicaltrials.gov, siltuximab has been investigated in the following clinical conditions:

- Siltuximab has been studied in combination with cytotoxic chemotherapy vs. chemotherapy alone in multiple myeloma. In both phase 2 trials, the addition of siltuximab did not provide additional benefit to chemotherapy alone.^{3,4}
- Lack of efficacy led to discontinuation of a phase 2 trial comparing siltuximab + BSC vs. placebo + BSC in anemic patients with low- or intermediate-1-risk Myelodysplastic Syndrome (MDS).⁵
- One trial noted a lack of clinical activity was noted in advanced solid tumors.
- A phase I/II trial noted the benefit of disease stabilization among patients with advanced renal cell cancer.

Safety⁶

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> None
Contraindications	<ul style="list-style-type: none"> Severe hypersensitivity reaction to siltuximab or any of its excipients. Excipients include: L-histidine, polysorbate 80, sucrose
Warnings/Precautions	<ul style="list-style-type: none"> Concurrent Active Severe Infections. Siltuximab may mask signs and symptoms of acute inflammation (suppression of fever and acute phase reactants such as C-reactive protein) and should not be given to patients with severe infections. Monitor patients closely for infections. Institute prompt anti-infective therapy and do not administer further siltuximab until the infection resolves. Vaccinations. Do not administer live vaccines because IL-6 inhibition may interfere with the normal immune response to new antigens. Infusion Related Reactions (IRR) and Hypersensitivity. Should a patient develop signs of anaphylaxis, stop the siltuximab infusion and discontinue further therapy. If a mild-moderate infusion reaction occurs, stop the infusion. When the reaction resolves, the infusion may be restarted at a lower rate. Continue premedication with antihistamines, acetaminophen and corticosteroids. Discontinue siltuximab if the patient does not tolerate the infusion following these interventions. Siltuximab should be administered in a setting that provides resuscitation equipment, medication and personnel trained in resuscitation procedures. Gastrointestinal (GI) Perforation. GI perforation has been reported in clinical trials, although not in MCD trials. Use siltuximab with caution in patients who may be at increased risk for GI perforation. Promptly evaluate symptoms suggestive of GI perforation.

Safety Considerations

- Although Grade 3/4 toxicities are not common with siltuximab, consideration should be given to the lower grade toxicities that were significantly greater with siltuximab vs. placebo. These include: pruritis (28 vs. 8%), upper respiratory tract infections (26 vs. 15%), hyperuricemia (11 vs. 0%), constipation (8 vs. 4%) and weight increase (19 vs. 0%).¹
- Due to the potential increase in risk of infection, careful patient selection should rule out active and/or chronic infections.
- IRR were reported in 4.8% of 249 patients treated with siltuximab. Of ~750 patients treated, only one experienced a Grade 3 anaphylactic reaction with the first infusion.⁷
- Long term exposure to siltuximab in MCD has been evaluated. Median exposure for 19 patients was 5.1 years (range, 3.4-7.2). No cumulative toxicities were noted with prolonged treatment.

Adverse Reactions

Common adverse reactions	Incidence \geq 10%: pruritus, increased weight, rash, hyperuricemia, upper respiratory tract infection
Death/Serious adverse reactions	Grade \geq 3 toxicities: fatigue 9%; night sweats 8%; generalized edema 8%
Discontinuations due to adverse reactions	23% vs. 38%, siltuximab vs. placebo, respectively; adverse events that led to discontinuation of siltuximab were mainly constitutional symptoms of CD; 4% vs. 15% died of disease progression (patients on placebo who did not cross over)

Drug Interactions

Drug-Drug Interactions

- Cytochrome P450s in the liver are down-regulated by cytokines such as IL-6. Inhibiting IL-6 signaling with siltuximab may increase CYP450 activity leading to increased metabolism of drugs that are substrates of CYP450. Therefore patients receiving CYP450 substrates with a narrow therapeutic index should have therapeutic monitoring of effect (e.g. warfarin) or drug concentrations (e.g. cyclosporine) and adjust dose as needed prior to starting or stopping siltuximab therapy. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy.

Risk Evaluation

As of January, 2016.

Comments

Sentinel event advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Siltuximab 100 mg and 400 mg lyophilized powder	Rituximab	None	None	Cetuximab Sunitinib
Sylvant	None	None	None	Sylatron Survanta

- (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- IL-6 antagonist therapy should be continued until disease progression. Evidence in one study with tocilizumab indicates that once therapy is stopped, symptoms of MCD can recur.

Outcome in clinically significant area	Durable tumor and symptomatic response, sustained for at least 18 weeks
Effect Size	Difference in outcomes between groups
Potential Harms	Grade 3 \geq toxicities: fatigue 9%, night sweats 8%, generalized edema 8%
Net Clinical Benefit	Substantial (high benefit with low risk of harm)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in \geq 20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration⁶

- Siltuximab dose is 11 mg/kg given over 1 hour as an intravenous infusion every 3 weeks until treatment failure.
- Perform hematology laboratory tests prior to each dose for the first 12 months and every 3 dosing cycles thereafter. If Hematology treatment criteria are not met, consider delaying treatment. Do not reduce dose.
- Refer to package insert for full dosing and administration information.

Treatment Criteria

Hematology parameter	Requirements before first dose	Retreatment criteria
ANC	$\geq 1.0 \times 10^9/\text{L}$	$\geq 1.0 \times 10^9/\text{L}$
Platelet count	$\geq 75 \times 10^9/\text{L}$	$\geq 50 \times 10^9/\text{L}$
Hemoglobin	$< 17 \text{ g/dL}$	$< 17 \text{ g/dL}$

Special Populations (Adults)⁶

	Comments
Elderly	<ul style="list-style-type: none"> • Within the clinical trial population, 35% of patients were 65 years and older. No differences in safety between older and younger patients were noted. Potential differences in efficacy cannot be determined as there were not enough patients in the older population.
Pregnancy	<ul style="list-style-type: none"> • Pregnancy Category C. There are no studies in pregnancy women. It is expected that siltuximab may cross the placenta and that infants born to women treated with siltuximab may be at increased risk of infection; caution is advised in the administration of live vaccines to these infants. Use in pregnancy is recommended only if the potential benefit justifies potential risk to the fetus. Advise patients of child-bearing potential to avoid pregnancy. Women of childbearing potential should use contraception during and for 3 months after treatment.
Lactation	<ul style="list-style-type: none"> • It is suspected that siltuximab may be excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Renal Impairment	<ul style="list-style-type: none"> • Based upon population PK analysis, no significant difference in clearance was observed in those with CrCl \geq 15 ml/min compared to those with baseline normal renal function of CrCl \geq 90ml/min.
Hepatic Impairment	<ul style="list-style-type: none"> • Based upon population PK analysis, no significant difference in clearance was observed in patients with mild – moderate hepatic impairment (Child-Pugh Classes A and B) compared to baseline normal hepatic function. No initial dose adjustment is necessary in these populations. Patients with severe hepatic impairment (C-P Class C) were not included in clinical trials.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified

Projected Place in Therapy ^{8, 9, 10, 11}

- Castleman’s Disease (CD) is not considered to be a malignancy. It is a lymphoproliferative disorder with an abnormal overgrowth of lymphocytes, similar to lymphomas and also known as angiofollicular lymph node hyperplasia. . Multicentric Castleman’s Disease (MCD) is a rare systemic disease, unlike Unicentric Castleman’s Disease (UCD) which is localized. There are three variants of CD: plasmacytic, hyaline vascular and mixed subtype. The hyaline vascular form can lead to clonal proliferation of lymphocytes and may evolve into non-Hodgkins lymphoma.
- Patients often experience peripheral lymphadenopathy, hepatosplenomegaly, fevers and night sweats. MCD has a strong association with immune suppression, particularly HIV, and HHV-8 infection.
- Pathogenesis of UCD and MCD has been associated with excessive IL-6, leading to constitutional symptoms, growth of B-lymphocytes and plasma cells and secretion of VEGF; MCD is commonly associated with HHV-8 infection.
- The median age of presentation is 50-65 years; HIV+ patients present at a younger age; 50-65% male.
- A rare disease is one that affects fewer than 200,000 Americans at any given time. Between FY14-FY15 roughly 900 unique Veteran patients with MCD were identified by the ICD-9 code 229.0.
- The prognosis of untreated MCD is poor. Median survival was 26 to 30 months.
- Siltuximab is the first FDA-approved drug to treat MCD. Tocilizumab and rituximab are not FDA-approved for this indication. Tocilizumab has had approval in Japan since 2005.
- Siltuximab is a life-long therapy that has the potential to improve patient-related outcomes among symptomatic patients with this rare disease.
- There is no standard of care for MCD. Subject matter experts who authored the MCD topic of UpToDate® prefer to treat with IL-6 antagonist-based therapy initially (siltuximab or tocilizumab) and consider rituximab as an alternative (GRADE 2B).
- The NCCN Guidelines recommend either siltuximab or rituximab +/- prednisone as initial treatment in patients with HIV(-), HHV-8(-) MCD. Following progression, the alternative is recommended. These recommendations are Category 2A (based upon a lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate).

References

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Appendix 1: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized studies essential • Blinding not essential 	<ul style="list-style-type: none"> • Universally accepted direct measure of benefit • Easily measured • Precisely measured 	<ul style="list-style-type: none"> • May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized blinded studies 	<ul style="list-style-type: none"> • Patient perspective of direct clinical benefit 	<ul style="list-style-type: none"> • Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression-Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.