

Siltuximab Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Indicator
Treatment of adult patients with Multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpes virus 8 (HHV-8) negative.	D47	00277a	ODMS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Treatment with siltuximab is administered once every 21 days until disease progression or unacceptable toxicity develops

Facilities to treat anaphylaxis MUST be present when siltuximab is administered

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Siltuximab	11mg/kg	IV	250mL glucose 5% over 60mins	Every 21 days
Administration sets lined with polyvinyl chloride (PVC) with di-(2-ethylhexyl)phthalate (DEHP) or polyurethane (PU), containing a 0.2 micron inline polyethersulfone (PES) filter should be used.					

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Grade 1 or greater disease symptoms

EXCLUSIONS:

- Hypersensitivity to siltuximab or any of the excipients
- Previous treatment with an interleukin-6 targeted treatment
- Clinically significant infections, including known hepatitis C infection or known to be hepatitis B surface antigen (HBsAg) positive.
- History of or concurrent lymphoma

Use with Caution:

- In patients who may be at increased risk of gastrointestinal perforation

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PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- Blood, renal and liver profile
- Virology screen -Hepatitis B* (HBsAg, HBcoreAb), Hepatitis C, HIV.
*Hepatitis B reactivation: See Adverse events/ Regimen specific complications

Regular tests:

- Blood, renal and liver profile monthly for first 12 months and every 3 dosing cycles thereafter.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- No dose adjustment required in elderly patients (> 65 years).
- Discontinuing the product should be considered if there are more than 2 dose delays due to toxicities related to the treatment during the first 48 weeks.

Haematological:

Table 1: Haematological criteria for treatment with siltuximab

Laboratory parameter	Requirements before first administration	Retreatment Criteria
ANC	$\geq 1 \times 10^9 / L$	$\geq 1 \times 10^9 / L$
Platelet Count	$\geq 75 \times 10^9 / L$	$\geq 50 \times 10^9 / L$
Haemoglobin*	<17g/dL	<17g/dL

*Siltuximab may increase haemoglobin levels in MCD patients

If the above treatment criteria are not met, consider delaying treatment with siltuximab for up to 3 weeks. Do not reduce dose.

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for siltuximab in patients with renal or hepatic impairment

Renal impairment	Hepatic impairment
No formal study of the effect of renal impairment on the pharmacokinetics of siltuximab has been conducted.	No formal study of the effect of hepatic impairment on the pharmacokinetics of siltuximab has been conducted.

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Non-haematological toxicity:

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Severe infection or non-haematological toxicity	Withhold dose until recovery and restart at same dose once resolved
Severe infusion related reactions, anaphylaxis, severe allergic reaction or cytokine release syndromes.	Discontinue treatment. Do not restart

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL : Minimal (**Refer to local policy**).

PREMEDICATIONS:

None usually required unless has suffered a previous hypersensitivity/infusion reaction.

OTHER SUPPORTIVE CARE:

- Inform patients that siltuximab may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.
- Advise patients of childbearing potential to avoid pregnancy which may include use of contraception during treatment and for 3 months after siltuximab therapy.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Concurrent Active Severe Infections:** Infections, including localised infections, should be treated prior to administration of siltuximab. Siltuximab may mask the signs and symptoms of acute inflammation including suppression of fever and of acute phase reactants such as C-reactive protein (CRP). Patients receiving siltuximab should be monitored closely for infections and prompt anti-infective therapy instituted if required.
- **Lipid parameters:** Elevations in triglycerides and cholesterol were observed in patients treated with siltuximab.
- **Infusion Related reactions and hypersensitivity:** Siltuximab was associated with an infusion related reaction or hypersensitivity reaction in 4.8% (severe reaction in 0.8%) of patients receiving siltuximab monotherapy in clinical trials. During intravenous infusion of siltuximab, mild to moderate infusion reactions may improve following slowing of or stopping the infusion. Upon resolution of the reaction, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, paracetamol, and corticosteroids may be considered. For patients who do not tolerate the infusion following these interventions, siltuximab should be discontinued. During or following infusion, treatment should be discontinued in patients who have severe infusion related hypersensitivity reactions (e.g., anaphylaxis). The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction.

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- **Gastrointestinal perforation:** Gastrointestinal (GI) perforation has been reported in clinical trials although not in MCD trials. Use with caution in patients who may be at increased risk for GI perforation. Promptly evaluate patients presenting with symptoms that may be associated or suggestive of GI perforation.
- **Liver Impairment:** There is not conclusive data about the possible association between siltuximab treatment and the development of abnormal liver function. It is advisable to monitor liver function during treatment.
- **Live, attenuated vaccines:** These should not be given concurrently or within 4 weeks before initiating siltuximab as clinical safety has not been established.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb (**as per local policy**). If either test is positive, such patients should be treated with anti-viral therapy. (**Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- No in vitro or in vivo drug-drug interaction studies have been conducted with siltuximab.
- Upon initiation or discontinuation of siltuximab therapy, in patients being treated with CYP450 substrates with a narrow therapeutic index, perform therapeutic monitoring of effect (e.g. warfarin) or drug concentration (e.g. cyclosporine or theophylline) as needed and adjust dose. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy.
- Exercise caution when siltuximab is co-administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable (e.g., oral contraceptives, lovastatin, atorvastatin).
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. van Rhee F, et al. [Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial](#). The Lancet Oncology. 2014; 15(9): 966-974.
2. Kurzock R et al. [A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease](#). Clin. Cancer Res. 2013; 19(13): 3659-3670.
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf>
4. Siltuximab (Sylvant™) Summary of Product Characteristics EMA Last updated: 12/05/2021 . Accessed Aug 2022 Available at https://www.ema.europa.eu/en/documents/product-information/sylvant-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/10/2015		Dr John Quinn
2	20/09/2017	Updated with new NCCP regimen template. Updated emetogenic potential as per NCCN guideline and clarified dosing for non-haematological toxicity	Dr John Quinn
3	13/11/2019	Reviewed.	Dr John Quinn
4	21/10/2022	Updated ICD 10 code . Updated baseline tests. Updated adverse events. Reviewed.	Dr John Quinn

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