1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SYLVANT® 100 mg (powder for concentrate for solution for infusion)

SYLVANT® 400 mg (powder for concentrate for solution for infusion)

2 QUALITIVE AND QUANTITIVE COMPOSITION

SYLVANT 100 mg vial: Each single use vial contains 100 mg siltuximab powder for concentrate for solution for infusion.

SYLVANT 400 mg vial: Each single use vial contains 400 mg siltuximab powder for concentrate for solution for infusion.

Contains sugar. (SYLVANT 100 mg contains 186 mg of sucrose per vial and SYLVANT 400 mg contains 711 mg of sucrose per vial).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

100 mg vial: The appearance of the lyophilised cake is a white solid with no meltback.

400 mg vial: The appearance of the lyophilised cake is a white solid with no meltback.

Once reconstituted, the solution is colourless and free of visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SYLVANT is 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.

4.2 Posology and method of administration

Posology

Dosage – 18 years and older

SYLVANT 11 mg/kg is given over 1 hour as an intravenous infusion administered every 3 weeks until treatment failure.

Haematology laboratory tests should be performed prior to each dose of SYLVANT therapy for the first 12 months and every 3 dosing cycles thereafter. The doctor should consider delaying treatment if the treatment criteria outlined in Table 1 are not met, before administering SYLVANT. Dose reduction is not recommended.

Table 1 Treatment Criteria

Laboratory parameter	**Requirements before first SYLVANT administration**	**Retreatment criteria**
Absolute Neutrophil Count	≥ 1,0 × 10^9/L	≥ 1,0 × 10^9/L
Platelet count	≥ 75 × 10^9/L	≥ 50 × 10^9/L
Haemoglobin[a]	< 170 g/L	< 170 g/L

[a] SYLVANT may increase haemoglobin levels in MCD patients.

SYLVANT therapy should be withheld if the patient has a severe infection or any severe non-haematological toxicity and can be restarted at the same dose after recovery.

If the patient develops a severe infusion related reaction, anaphylaxis, severe allergic reaction, or cytokine release syndrome related to SYLVANT infusion, further administration of SYLVANT should be discontinued.

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.

Special populations

Elderly 65 years of age and older

No major age-related differences in pharmacokinetic (PK) or in safety profile were observed in clinical studies. No dose adjustment is required (see section 5.2).

Renal impairment

No formal studies have been conducted to investigate the pharmacokinetics of SYLVANT in patients with renal impairment. (see section 5.2).

Hepatic impairment

No formal studies have been conducted to investigate the pharmacokinetics of SYLVANT in patients with hepatic impairment. (see section 5.2.

Paediatric population (17 years of age and younger)

The safety and efficacy of SYLVANT have not been established in paediatric patients.

Method of administration

Intravenous infusion (I.V.) of SYLVANT should be administered by qualified healthcare professionals.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Concurrent active serious infections

Infections, including localised infections, should be treated prior to administration of SYLVANT. Serious infections including pneumonia and sepsis were observed during clinical studies (see section 4.8).

SYLVANT may mask signs and symptoms of acute inflammation including suppression of fever and of acute phase reactants such as C-reactive protein (CRP). Therefore, doctors should diligently monitor patients receiving treatment in order to detect serious infections.

Vaccinations

Live, attenuated vaccines should not be given concurrently or within 4 weeks before initiating SYLVANT, because clinical safety has not been established and because IL-6 inhibition may interfere with the normal immune response to new antigens.

Lipid parameters

Elevations in triglycerides and cholesterol (lipid parameters) were observed in patients treated with SYLVANT (see section 4.8). Patients should be managed according to current clinical guidelines for management of hyperlipidaemia.

Infusion related reactions and hypersensitivity

During I.V. infusion of SYLVANT, mild to moderate infusion reactions may occur. Upon resolution of the reaction, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, acetaminophen, and corticosteroids may be considered. For patients who do not tolerate the infusion following these interventions, SYLVANT should be discontinued. During or following infusion, treatment with SYLVANT 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. Appropriate personnel and medicine should be available to treat anaphylaxis if it occurs (see section 4.8).

Malignancy

SYLVANT may increase the risk of malignancy. On the basis of limited experience with siltuximab the present data do not suggest any increased risk of malignancy.

Gastrointestinal perforation

Gastrointestinal (GI) perforation has been reported in SYLVANT clinical 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.

Hepatic impairment

Following treatment with SYLVANT in clinical trials, transient or intermittent mild-to-moderate elevation of hepatic transaminases or other liver function tests such as bilirubin have been reported. SYLVANT – treated patients with known hepatic impairment as well as patients with elevated transaminase or bilirubin levels should be monitored.

4.5 Interaction with other medicines and other forms of Interaction

No formal interaction studies have been conducted with SYLVANT.

In nonclinical studies, IL-6 is known to decrease the activity of cytochrome P450 (CYP450). Binding bioactive IL-6 by siltuximab may result in increased metabolism of CYP450 substrates, because CYP450 enzyme activity will normalise. Therefore, administering SYLVANT with CYP450 substrates that have a narrow therapeutic index has the potential to change medicine therapeutic effects and toxicity due to alterations in the CYP450 pathways. Upon initiation or discontinuation of SYLVANT in patients being treated with concomitant medications that are CYP450 substrates and have a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or medicine concentration (e.g., ciclosporin or theophylline) is recommended. The dose of the concomitant medication should be adjusted as needed. The effect of SYLVANT on CYP450 enzyme activity can persist for several weeks after stopping therapy. Doctors should also exercise caution when SYLVANT is co administered with CYP3A4 substrate medicines where a decrease in effectiveness would be undesirable (e.g., oral contraceptives).

Paediatric population

No interaction studies have been performed in this population.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment (see section 4.5).

Pregnancy

There are no data from the use of SYLVANT in pregnant women. Studies in animals with siltuximab have shown no adverse effect on pregnancy or on embryofetal development.

The safety of SYLVANT in pregnancy has not been established.

SYLVANT is contraindicated in pregnancy.

It is not known whether siltuximab can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity.

Doctors should also exercise caution when SYLVANT is administered with CYP3A4 substrates where a decrease in effectiveness would be undesirable e.g. oral contraceptives (see section 4.5). Siltuximab crosses the placenta, as was observed in studies in monkeys. Consequently, infants born to women treated with SYLVANT may be at increased risk of infection, and caution is advised in the administration of live vaccines to these infants (see section 4.4).

Breastfeeding

The safety of SYLVANT in lactation has not been established. Women should not breastfeed their babies while taking SYLVANT. It is not known whether siltuximab or its metabolites are excreted in human milk.

Fertility

Effects of siltuximab on fertility have not been evaluated in humans. Available non-clinical data do not suggest an effect on fertility under siltuximab treatment.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

Sylvant has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent side effects (> 20 % of patients) during treatment with SYLVANT in the MCD clinical trials were upper respiratory tract infection, pruritus, rash, arthralgia and diarrhoea. The most serious side effect associated with the use of SYLVANT was anaphylactic reaction.

Tabulated list of adverse reactions

Table 2 lists adverse reactions observed in MCD patients treated with SYLVANT at the recommended dosage of 11 mg/kg every 3 weeks. Within the system organ class, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10000 and < 1/1000); very rare (< 1/10000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in SYLVANT treated patients in MCD clinical studies[a]

System organ class Frequency	**Adverse reaction**
Infections and infestations	
very common	Upper respiratory tract infection, urinary tract infection, nasopharyngitis
Blood and lymphatic system disorders	
very common	Neutropenia, thrombocytopenia
Immune system disorders	
common	Anaphylactic reaction

Metabolism and nutrition disorders	
very common	Hypertriglyceridaemia, hyperuricaemia
common	Hypercholesterolaemia
Nervous system disorders	
very common	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	
very common	Oropharyngeal pain
Vascular disorders	
very common	Hypertension
Gastrointestinal disorders	
very common	Nausea, abdominal pain, vomiting, constipation, diarrhoea, gastroesophageal reflux disease, mouth ulceration
Skin and subcutaneous tissue disorders	
very common	Rash, pruritus, eczema
Musculoskeletal and connective tissue disorders	
very common	Arthralgia, pain in extremity
Renal and urinary disorders	
very common	Renal impairment
General disorders and administration site conditions	
very common	Localised oedema
Investigations	
very common	Weight increased

[a] All patients with CD treated with SYLVANT at recommended dose of 11 mg/kg every 3 weeks [including crossover patients (N = 87)]

Description of selected adverse reactions

Infusion related reactions and hypersensitivity:

In clinical studies, SYLVANT was associated with an infusion related reaction or hypersensitivity reaction in 5,1 % (severe reaction in 0,8 %) of patients treated with SYLVANT monotherapy.

In long-term treatment of MCD patients with SYLVANT at the recommended dosage of 11 mg/kg every 3 weeks, infusion related reactions or hypersensitivity reactions occurred at a frequency of 6,3 % (1,3 % for severe reactions).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No case of overdose has been reported. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION: A.30.1 Antibodies

Pharmacotherapeutic group and ATC code: Immunosuppresants, interleukin inhibitors, ATC code: L04AC11.

Mechanism of action:

Siltuximab is a chimeric (human murine) monoclonal antibody against human Interleukin-6 (IL 6) produced in a Chinese Hamster Ovary (CHO) cell line. Siltuximab forms stable complexes with soluble bioactive forms of human interleukin 6 (IL-6), thereby preventing the binding of human IL-6 to both soluble and membrane-bound IL-6 receptors (IL-6R), thus inhibiting several processes mediated by IL-6. This includes inhibition of immunoglobulin secretion, hepatic acute phase protein synthesis, and haematopoietic precursor cell proliferation and differentiation. Overproduction of IL-6, in chronic inflammatory diseases and malignancies has been linked to anaemia and cachexia and has been hypothesised to play a central role in driving plasma cell proliferation and systemic manifestations in patients with Crohn's disease (CD).

5.2 Pharmacokinetic properties

Following the first administration of siltuximab (doses ranging from 0,9 to 15 mg/kg), the area under the concentration-time curve (AUC) and maximal serum concentration (C_{max}) increased in a dose-proportional manner and clearance (CL) was independent of dose. Following the single dose administration at the recommended dose regimen (11 mg/kg given once every 3 weeks), the clearance was 3,54 ± 0,44 mL/kg/day and half-life was 16,3 ± 4,2 days. Following the repeat dose administration at the recommended dose, siltuximab clearance and systemic accumulation was observed (accumulation index of 1,7). Consistent with half-life after the first dose, serum concentrations reached steady-state levels by the sixth every 3-week infusion with mean (± SD) peak and trough concentrations of 332 ± 139 and 84 ± 66 mcg/mL, respectively.

Immunogenicity

In clinical studies, including single agent and combination studies 4 of 432 (0,9 %) evaluable patients tested positive for anti siltuximab antibodies. Further immunogenicity analyses were

conducted for all positive samples from the 4 patients with detectable anti-siltuximab antibodies. None of these patients had neutralising antibodies. No evidence of altered safety or efficacy was identified in the patients who developed antibodies to siltuximab.

Paediatrics 17 years of age and younger

The safety and efficacy of siltuximab have not been established in paediatric patients.

Elderly 65 years of age and older

The population of siltuximab was analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics (PK) of siltuximab in patients older than 65 years.

Renal impairment

For subjects with baseline calculated creatinine clearance of 12 mL/min or greater, there was no meaningful effect on siltuximab PK. Four patients with severe renal impairment (creatinine clearance 12 to 30 mL/min) were included in the data set.

Hepatic impairment

For subjects with baseline alanine transaminase ranging from 0,1 to 3,7 times the upper limit of normal and baseline albumin ranging from 1,5 to 5,8 g/dL, there was no meaningful effect on siltuximab PK.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SYLVANT contains *L*-Histidine, *L*-Histidine monohydrochloride monohydrate, polysorbate-80 and sucrose.

Contains sugar. (SYLVANT 100 mg contains 186 mg of sucrose per vial and SYLVANT 400 mg contains 711 mg of sucrose per vial).

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

Unopened vial: 36 months.

After reconstitution and dilution:

Chemical and physical in-use stability has been demonstrated for up to 8 hours at room temperature (see section 6.6).

From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Store between 2 to 8 °C in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

100 mg vial: The product is supplied (as a sterile, single-use lyophilised dosage form) in an 8R (8 mL) Type I clear colourless glass vial closed with a fluoropolymer coated 20 mm lyophilisation-type mist-grey stopper and a 20 mm silver aluminum seal with a flip-off button, packed in an outer carton.

400 mg vial: The product is supplied (as a sterile, single-use lyophilised dosage form) in a 30 mL Type I clear colourless glass vial closed with a fluoropolymer film

coated 20 mm lyophilisation-type garnet stopper and a 20 mm silver aluminum seal with a flip-off button, packed in an outer carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

This product is for single use only.

Use aseptic technique

1. Calculate the dose, total volume of reconstituted SYLVANT solution required and the number of vials needed. The recommended needle for preparation is 21 - gauge 1 - ½ inch (38 mm). Infusion bags (250 mL) must contain Dextrose 5 % and must be made of polyvinyl chloride (PVC), or polyolefin (PO), or polypropylene (PP) or polyethylene (PE). Alternatively, PE bottles may be used.
2. Allow vial(s) of SYLVANT to come to room temperature over approximately 30 minutes. SYLVANT should remain at room temperature for the duration of the preparation.

   For 100 mg and 400 mg vials: Each vial should/must be reconstituted as instructed in Table 3.

   Table 3: Reconstitution Instructions

Strength	Amount of Sterile Water for Injection, required for reconstitution	Post-reconstitution concentration
100 mg vial	5,2 mL	20 mg/mL
400 mg vial	20,0 mL	20 mg/mL

   Gently swirl (DO NOT SHAKE or VORTEX or SWIRL VIGOROUSLY) the reconstituted vials to aid the dissolution of the lyophilised powder. Do not remove contents until all of the solids have been completely dissolved. The lyophilised

powder should dissolve in less than 60 minutes. Inspect the vials for particulate matter and discolouration prior to dose preparation. Do not use if visibly opaque or foreign particles and/or solution discolouration are present. Dilute the total volume of the reconstituted SYLVANT solution dose to 250 mL with sterile Dextrose 5 %, by withdrawing a volume equal to the volume of reconstituted SYLVANT from the Dextrose 5 %, 250 mL bag.

Slowly add the total volume of reconstituted SYLVANT solution to the 250 mL infusion bag. Gently mix.

3. The reconstituted product SYLVANT should be kept for no more than two hours prior to addition into the IV bag. The infusion should be completed within 6 hours of the addition of the reconstituted solution to the infusion bag.

   Administer the diluted solution over a period of 1 hour using administration sets lined with PVC or polyurethane (PU), or PE containing a 0,2-micron inline polyethersulfone (PES) filter. SYLVANT does not contain preservatives; therefore, do not store any unused portion of the infusion solution for reuse.
4. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of SYLVANT with other agents. Do not infuse SYLVANT concomitantly in the same intravenous line with other agents.
5. Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 Eleventh Avenue

Houghton Estate, 2198

South Africa

8 REGISTRATION NUMBER(S)

100 mg: 49/30.1/0098

400 mg: 49/30.1/0099

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 December 2019

10 DATE OF REVISION OF TEXT

21 May 2025