SYLVANT®

Siltuximab

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SYLVANT 100 mg powder for infusion concentrate

SYLVANT 400 mg powder for infusion concentrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYLVANT is a chimeric (human murine) immunoglobulin G1k (IgG1k) monoclonal antibody against human Interleukin-6 (IL-6) produced in a Chinese Hamster Ovary (CHO) cell line.

SYLVANT 100 mg powder for infusion concentrate

Each single use vial contains 100 mg siltuximab powder for concentrate for solution for infusion. After reconstitution the solution contains 20 mg siltuximab per mL.

SYLVANT 400 mg powder for infusion concentrate

Each single use vial contains 400 mg siltuximab powder for concentrate for solution for infusion. After reconstitution the solution contains 20 mg siltuximab per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for infusion concentrate.

The product is a freeze-dried white powder.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SYLVANT is indicated for the treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Intravenous infusion (IV) of SYLVANT should be administered by qualified healthcare professionals. Appropriate personnel and medicinal product should be available to treat anaphylaxis if it occurs.

Treatment criteria

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 prescriber 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 × 109/L	≥ 1.0 × 109/L
Platelet count	≥ 75 × 109/L	≥ 50 × 109/L
Haemoglobina	< 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 nonhaematological 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

Renal Impairment

No formal studies have been conducted to investigate the pharmacokinetics of SYLVANT in patients with renal impairment. No dose adjustments can be recommended (see section 4.4).

Hepatic Impairment

No formal studies have been conducted to investigate the pharmacokinetics of SYLVANT in patients with hepatic impairment. No dose adjustments can be recommended (see section 4.4).

Method of administration

SYLVANT must be administered as an intravenous infusion.

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. See **section 6.1**.

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***).*

Hypoglobulinaemia was observed in 4 to 11.3% of patients in the clinical study. Decreases in total IgG, IgA, or IgM levels below normal were observed in the range of 4 to 11% patients in the MCD trial (Study 1).

All clinical studies with SYLVANT excluded patients with clinically significant infections, including those known to be hepatitis B surface antigen positive. Two cases of reactivated hepatitis B have been reported when SYLVANT was administered concomitantly with high dose dexamethasone, and bortezomib, melphalan and prednisone in multiple myeloma patients.

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, prescribers 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 IV infusion of SYLVANT, 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, 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 medication should be available to treat anaphylaxis if it occurs (see **section 4.8**).

Appropriate personnel and medicinal product should be available to treat anaphylaxis if it occurs.

Malignancy

Immunomodulatory drugs 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 siltuximab 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.

Pancreatitis

Cases of pancreatitis have been reported with other interlukein-6 inhibitors.

Special populations

Paediatric Use

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

Use in the Elderly

The population PK of siltuximab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the PK of siltuximab in patients older than 65 years. No major age related differences in pharmacokinetic (PK) or in safety profile were observed in clinical studies. No dose adjustment is required.

Renal Impairment

No formal studies have been conducted to investigate the pharmacokinetics of SYLVANT in patients with 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

No formal studies have been conducted to investigate the pharmacokinetics of SYLVANT in patients with 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.

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug-drug 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 drug 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 drug concentration (e.g., cyclosporine 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. Prescribers should also exercise caution when SYLVANT is co-administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable (e.g., oral contraceptives).

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category C

There are no data from the use of SYLVANT in pregnant women. No maternal or foetal toxicity was observed in cynomolgus monkeys after intravenous administration of siltuximab. It is not known whether siltuximab can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. SYLVANT should be given to a pregnant woman only if the benefit clearly outweighs the risk. Women of childbearing potential must use effective contraception during and up to 3 months after treatment. Prescribers 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**). As with other immunoglobulin G antibodies, siltuximab crosses the placenta as 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.

Breast-feeding

It is not known whether siltuximab or its metabolites are excreted in human milk. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SYLVANT, 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.

Fertility

Effects of siltuximab on fertility have not been evaluated in human patients. In cynomolgus monkeys dosed intravenously with siltuximab, no histopathological changes were noted in the reproductive tissues. In mice dosed subcutaneously with an anti-mouse IL-6 monoclonal antibody, no effects on male or female fertility were observed.

4.7 EFFECT ON ABILITY TO DRIVE AND OPERATE MACHINERY

No studies of the effects on the ability to drive and use machines have been performed. It is not known if SYLVANT has an effect on motor skills.

4.8 UNDESIRABLE EFFECTS

Data from all patients treated with SYLVANT monotherapy (n=370) form the overall basis of the safety evaluation.

Table 2 reflects the frequencies of identified adverse reactions in the 87 MCD patients (Study 1, Study 2 and Study 3) treated at the recommended dosage of 11 mg/kg every 3 weeks.

- In Study 1, a randomised placebo controlled Phase 2 study in (MCD), 53 patients were randomised to the SYLVANT treatment arm and treated at the recommended dose, 11/mg/kg, every 3 weeks and 26 patients were randomised to the placebo arm. Of the 26 placebo-treated patients, 18 patients subsequently crossed-over to receive SYLVANT.
- In Study 2, a Phase 1 study, 16 of 37 patients with CD were treated with SYLVANT, at the recommended dosage of 11 mg/kg every 3 weeks.
- In Study 3, an open-label, multicenter, non-randomized Phase 2 study in 60 patients with MCD who were previously enrolled in Study 1 (41 patients) or Study 2 (19 patients), patients were treated with siltuximab, at the recommended dosage of 11 mg/kg every 3 weeks.

The most frequent adverse reactions (> 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 adverse reaction associated with the use of SYLVANT was anaphlyactic reaction.

Adverse reactions observed in MCD patients treated with SYLVANT at the recommended dosage of 11 mg/kg every 3 weeks are summarised in **Table 2**.

Table 2: Adverse Reactions in SYLVANT Treated Patients in MCD Clinical Studies

	SYLVANT + BSC[a] N=87		**Placebo + BSC[b] N=26**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Infections and infestations				

Nasopharyngitis	17.2%	0.0%	3.8%	0.0%
Upper respiratory tract infection	42.5%	0.0%	15.4%	3.8%
Urinary tract infection	10.3%	0.0%	0.0%	0.0%
Blood and lymphatic system disorders				
Neutropenia	10.3%	3.4%	7.7%	3.8%
Thrombocytopenia	12.6%	2.3%	3.8%	3.8%
Immune system disorders				
Anaphylactic reaction	1.1%	1.1%	0.0%	0.0%
	SYLVANT + BSC[a] N=87		**Placebo + BSC[b] N=26**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders				
Hypertriglyceridemia	17.2%	2.3%	0.0%	0.0%
Hyperuricemia	13.8%	3.4%	0.0%	0.0%
Hypercholesterolemia	9.2%	0.0%	0.0%	0.0%
Nervous system disorders				
Dizziness	19.5%	1.1%	7.7%	0.0%
Headache	13.8%	1.1%	3.8%	0.0%
Vascular disorders				
Hypertension	18.4%	8.0%	3.8%	0.0%
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	13.8%	0.0%	3.8%	0.0%
Gastrointestinal disorders				
Nausea	19.5%	4.6%	19.2%	0.0%
Abdominal pain	15.9%	0.0%	3.8%	3.8%
Vomiting	17.2%	3.4%	7.7%	0.0%
Constipation	19.5%	0.0%	3.8%	0.0%
Diarrhea	28.7%	1.1%	19.2%	3.8%
Gastroesophageal reflux disease	10.3%	0.0%	0.0%	0.0%
Mouth ulceration	13.8%	0.0%	3.8%	0.0%
Skin and subcutaneous tissue disorders				
Rash	21.8%	0.0%	3.8%	0.0%

Pruritus	32.2%	0.0%	15.4%	0.0%
Eczema	11.5%	0.0%	0.0%	0.0%
Musculoskeletal and connective tissue disorders				
Arthralgia	20.7%	0.0%	7.7%	0.0%
Pain in extremity	10.3%	0.0%	0.0%	0.0%
Renal and urinary disorders				
Renal impairment	10.3%	2.3%	0.0%	0.0%
General disorders and administration site conditions				
Localised oedema	14.9%	2.3%	3.8%	0.0%
Investigations				
Weight increased	17.2%	2.3%	0.0%	0.0%

[a]All patients with CD treated with SYLVANT at recommended dosage of 11 mg/kg every 3 weeks [including crossover patients (N=87)], BSC=Best Supportive Care

[b]All patients with CD treated with placebo (N=26)

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 siltuximab 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 asked to report any suspected adverse reactions: https://pophealth.my.site.com/carmreportnz/s/

4.9 OVERDOSE

No case of overdose has been reported. Repeated dosing of 15 mg/kg every 3 weeks has been administered without additional adverse drug reactions.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Siltuximab is a human-mouse chimeric monoclonal antibody that forms high affinity, stable complexes with soluble bioactive forms of human IL-6. Siltuximab prevents the binding of human IL-6 to both soluble and membrane-bound IL-6 receptors (IL-6R), thus inhibiting the formation of the hexameric signalling complex with gp130 on the cell surface. IL-6 is a pleiotropic

proinflammatory cytokine produced by a variety of cell types including T and B- cells, lymphocytes, monocytes and fibroblasts, as well as malignant cells. IL-6 has been shown to be involved in diverse normal physiologic processes such as induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic 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 CD.

Pharmacodynamic effects

In vitro, Siltuximab dose-dependently inhibited the growth of an IL-6-dependent murine plasmacytoma cell line in response to human IL-6. In cultures of human hepatoma cells, IL-6 stimulated production of the acute phase protein serum amyloid A was dose-dependently inhibited by siltuximab. Similarly, in cultures of human Burkitt's B-lymphoma cells, the production of immunoglobulin M (IgM) protein in response to IL-6 was dose-dependently inhibited by siltuximab.

Biomarkers

It is well established that IL-6 stimulates the acute phase expression of C-reactive protein (CRP). The mechanism of action of siltuximab is neutralisation of IL-6 bioactivity, which can be measured indirectly by suppression of CRP. Siltuximab treatment in MCD results in rapid and sustained decreases in CRP serum concentrations. Measurement of IL-6 concentrations in serum or plasma during treatment should not be used as a pharmacodynamic marker, as siltuximab-neutralised antibody-IL-6 complexes interfere with current immunological-based IL-6 quantification methods.

Clinical Efficacy and Safety

Study 1

A Phase 2, multinational, randomised (2:1) double blind, placebo controlled study was conducted to assess the efficacy and safety of SYLVANT (11 mg/kg every 3 weeks) compared with placebo in combination with best supportive care in patients with MCD. Treatment was continued until treatment failure (defined as disease progression based on increase in symptoms, radiologic progression or deterioration in performance status) or unacceptable toxicity. A total of 79 patients with symptomatic MCD were randomised and treated. Median age was 47 years (range 20-74) in the SYLVANT arm and 48 years (range 27-78) in the placebo arm. More male patients were enrolled in the placebo arm (85% in placebo vs. 56% in SYLVANT arm). ECOG performance status score (0/1/2) at baseline was 42%/45%/13% in SYLVANT arm and 39%/62/0% in the placebo arm respectively. At baseline 55% of patients in the SYLVANT arm and 65% of patients in the placebo arm had received prior systemic therapies for MCD and 30% of patients in the SYLVANT arm and 31% in the placebo arm were using corticosteroids. Histological subtype was similar in both treatment arms, with 33% hyaline vascular subtype, 23% plasmacytic subtype and 44% mixed subtype. Disease related baseline laboratory parameters are summarised in **Table 3**. CRP and erythrocyte sedimentation rate (ESR) showed wide variability across both treatment arms.

Table 3: Disease Related Baseline Laboratory Parameters

	SYLVANT + BSC	**Placebo + BSC**
Patients in Intent To Treat population	53	26
Haemoglobin (g/L) Mean (SD)	115.8 (24.70)	130.0 (25.70)
Platelets (109/L) Mean (SD)	323.2 (156.58)	302.6 (123.54)
Albumin (g/dL) Mean (SD)	3 5 (0.76)	3.6 (0.46)

ESR (mm/hr) Mean (SD)	68.3 (48.66)	34.6 (35.06)
CRP (mg/L) Mean (SD)	43.2 (53.63)	24.8 (34.53)
Fibrinogen (µmol/L) Mean (SD)	16.9 (7.52)	15.3 (7.48)

The primary endpoint of the study was durable tumour and symptomatic response, defined as tumour response assessed by independent review and complete resolution or stabilisation of prospectively collected MCD symptoms, for at least 18 weeks without treatment failure.

Study 1 demonstrated a statistically significant improvement in independently reviewed durable tumour and symptomatic response rate in the SYLVANT arm compared with the placebo arm (34% vs. 0%, respectively; 95% CI: 11.1, 54.8; p=0.0012). Sensitivity analyses further supported the primary endpoint analysis showing a significantly higher investigator assessed durable tumour and symptom response rate of 45% in SYLVANT treated patients compared with 0% in placebo treated patients (p <0.0001). The overall tumour response rate was evaluated based on modified Cheson criteria both by independent review and investigator assessment.

Key efficacy results from Study 1 are summarised in **Table 4**.

Table 4: Efficacy Endpoints From Study 1

Efficacy Endpoints	**SYLVANT+BSC[a]**	**Placebo+BSC**	**p-value[b]**
Primary Efficacy Endpoint			
Durable tumour & symptomatic response (independent review)	18/53 (34.0%)	0/26 (0%)	0.0012
Secondary Efficacy Endpoints			
Best tumour response (independent review	20/53 (37.7%)	1/26 (3.8%)	0.0022
Best tumour response (investigator assessment)	27/53 (50.9%)	0/26 (0%)	<0.0001
Time to treatment failure	Not reached	134 days	0.0084; HR 0.418
Haemoglobin increase >15 g/L at Week 13/haemoglobin response-evaluable population	19/31 (61.3%)	0/11 (0%)	0.0002
Duration of tumour & symptomatic response (days) - independent review; median (min, max)	340 (55, 676)[c]	N/A[d]	
Durable complete symptomatic response[e]	13/53 (24.5%)	0/26 (0%)	0.0037
Duration of durable complete symptomatic response (days) median (min, max)	472 (169, 762)[f]	N/A[c]	
Efficacy Endpoints	**SYLVANT+BSC[a]**	**Placebo+BSC**	**p-value[b]**

[a] Best Supportive Care

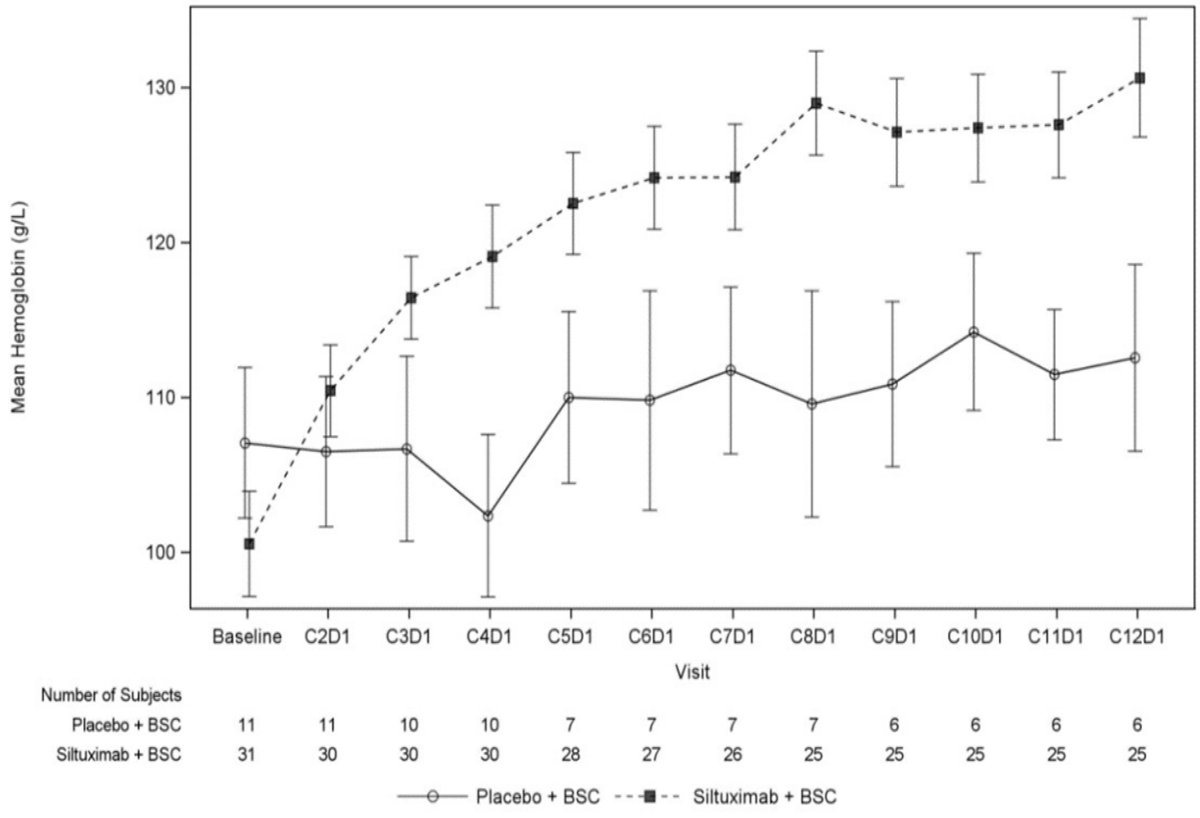
[b] Adjusted for corticosteroid use at randomisation [c] At the time of primary analysis data for 19 of 20 tumour and symptomatic responders were censored due to ongoing response

[d] N/A="Not applicable", there were no responders in the placebo arm, therefore, duration is not applicable [e] Complete symptomatic response is defined as a 100% reduction in the baseline MCD overall symptom score sustained for at least 18 weeks prior to treatment failure [f] Data from 11 of 13 durable complete symptomatic responders were censored due to on-going response

MCD-related signs and symptoms were prospectively collected. A total score of all symptoms (referred to as the MCD-related Overall Symptom Score) is the sum of the severity grades (NCI-CTCAE grade) of the MCD-related signs and symptoms [general MCD-related (fatigue, malaise, hyperhidrosis, night sweats, fever, weight loss, anorexia, tumour pain, dyspnoea, and pruritus) autoimmune phenomena, fluid retention, neuropathy, and skin disorders] and was calculated. The percent change from baseline in MCD-related signs and symptoms and MCD-related overall symptom score at each cycle was calculated. Complete symptom response was defined as a 100% reduction from the baseline in the MCD related overall symptom score sustained for at least 18 weeks prior to treatment failure.

Haemoglobin response was defined as a change from baseline of ≥ 15g/L at week 13. Mean haemoglobin by cycle during the blinded treatment period is presented in **Figure 1**.

Figure 1: Mean haemoglobin by cycle during the blinded treatment period



One-year survival rate was 100% in the SYLVANT arm and 92% in the placebo arm.

Subgroup analyses:

Analyses for both primary and secondary endpoints on various subgroups including age (<65 years and ≥ 65 years); race (White and non-White); region (North America, EMEA, and Asia

Pacific); baseline corticosteroid use (yes and no); prior therapy (yes and no); and MCD histology (plasmatic and mixed histology) consistently showed that the treatment effect favoured the SYLVANT arm except for the hyaline vascular subgroup. A consistent treatment effect favouring SYLVANT treated patients across all major secondary endpoints was shown - in the hyaline vascular subgroup. Select efficacy results from Study 1 in the hyaline vascular subgroup are summarised in **Table 5**.

Table 5: Select Efficacy Endpoints for Hyaline Vascular Subgroup from Study 1

Efficacy endpoints	SYLVANT+BSC	Placebo+BSC	95% CI[a]
Primary efficacy endpoint			
Durable tumour & symptomatic response (independent review)	0/18 (0%)	0/8 (0%)	(N/A, N/A)[b]
Secondary efficacy endpoints			
Durable tumour & symptomatic response (investigator review)	3/18 (16.7%)	0/8 (0%)	(-25.7; 55.9)
Best tumour response (independent review)	1/18 (5.6%)	1/8 (12.5%)	(-46.7; 35.3)
Best tumour response (investigator assessment)	4/18 (22.2%)	0/8 (0%)	(-20.3; 60.6)
Time to treatment failure	206 days	70 days	(0.17; 1.13)[c]
Haemoglobin increase > 15 g/L at Week 13/haemoglobin response-evaluable population	3/7 (42.9%)	0/4 (0%)	(-22.7; 83.7)
Durable complete symptomatic response[d]	3/18 (16.7%)	0/8 (0%)	(-25.7; 55.9)

[a] 95% confidence interval for the for the difference in proportions [b] N/A = "Not applicable", there were no responders therefore 95% CI is not applicable [c] 95% confidence interval for the hazard ratio

[d] Complete symptomatic response is defined as a 100% reduction in the baseline MCD overall symptom score sustained for at least 18 weeks prior to treatment failure

Study 2

In addition to Study 1 efficacy data are available in patients with CD from a single arm Phase 1 study (Study 2). In this study 37 patients with were treated with SYLVANT. 35 of whom had MCD. In total, 16 patients with MCD were treated with 11 mg/kg every 3 weeks. Patient demographics and disease characteristics for patients treated at 11 mg/kg every 3 weeks were similar to those in Study 1. Median age was 51 years (21-76) and 50% were male. ECOG performance status score (0/1/2) at baseline was 6%/69%/25% respectively. Sixty-nine percent of patients had received prior systemic therapies for MCD. Histological subtype was 44% hyaline vascular subtype, 50% plasmacytic subtype and 6% mixed subtype. The mean (SD) haemoglobin level was 125 (23) g/L.

The clinical benefit observed in Study 1 was supported by Study 2. Median duration of SYLVANT treatment was 1278 days and mean number of SYLVANT administrations was 51 in SYLVANT patients. In the 16 patients with MCD treated with 11 mg/kg every 3 weeks, overall tumour

response rate by independent review was 43.8% with 6.3% complete response. All tumour responses were durable for > 18 weeks. For patients with haemoglobin below lower limit of normal at baseline, the haemoglobin response rate at Week 13 was 50%. The 1-year survival rate of SYLVANT treated patients was 100%.

Study 3

An open-label, multicenter, non-randomized Phase 2 study assessed the safety and efficacy of extended treatment with siltuximab in 60 patients with MCD who were previously enrolled in Study CNTO328MCD2001 (41 patients) or Study C0328T03 (19 patients). Median duration of siltuximab treatment was 5.52 years (range: 0.8 to 10.8 years); more than 50% of patients received siltuximab treatment for ≥5 years. After a median of 6 years of follow-up, none of the 60 patients had died and maintenance of disease control was demonstrated in 58 of 60 patients.

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 was found to be timeinvariant, and systemic accumulation was moderate (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

As with all therapeutic proteins, there is potential for the generation of anti-drug antibodies (immunogenicity). The immunogenicity of siltuximab has been evaluated using antigen-bridging enzyme immunoassay (EIA) and electrochemiluminescence (ECL)-based immunoassay (ECLIA) methods.

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 neutralizing antibodies. No evidence of altered safety or efficacy was identified in the patients who developed antibodies to siltuximab.

Special populations

Cross-study population PK analyses were performed using data from 378 patients with a variety of conditions, who received single-agent siltuximab at doses ranging from 0.9 to 15 mg/kg. The effects of various covariates on siltuximab pharmacokinetics were assessed in the analyses.

Siltuximab clearance increased with increasing body weight; however, no dose adjustment is required for body weight since administration is on an mg/kg basis. The following factors had no clinical effect on the clearance of siltuximab: gender, age, ethnicity and use of corticosteroids. The effect of anti-siltuximab antibody status was not examined as there were insufficient numbers of anti-siltuximab antibody positive patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Formal genotoxicity studies have not been performed for siltuximab.

Carcinogenicity

Formal carcinogenicity studies have not been performed for siltuximab.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine

Polysorbate-80 Sucrose.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

36 months

After reconstitution and dilution

Chemical and physical in use stability has been demonstrated for 8 hours at room temperature. Unless the method of opening / reconstitution / dilution precludes the risk of microbial contamination, the product should be used immediately after reconstitution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light. Keep out of the sight and reach of children.

For storage conditions after reconstitution and dilution of the medicinal product, see **section 6.3**.

6.5 NATURE AND CONTENTS OF CONTAINER

SYLVANT 100 mg powder for infusion concentrate

The product is supplied (as a sterile, single-use lyophilised dosage form) in an 8 mL Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button.

SYLVANT 400 mg powder for infusion concentrate

The product is supplied (as a sterile, single-use lyophilised dosage form) in an 30 mL Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

This product is for single use only.

1. Use aseptic technique
2. 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. Infusion bags (250 mL) must contain Dextrose 5% and must be made of made of Polyvinyl chloride (PVC), or Polyolefin (PO), or polypropylene (PP), or polyethylene (PE). Alternatively, PE bottles may be used.
3. 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 6**.

Table 6: 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 discoloration prior to dose preparation. Do not use if visibly opaque or foreign particles and/or solution discoloration 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.

4. 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.
5. No physical biochemical compatibility studies have been conducted to evaluate the coadministration of SYLVANT with other agents. Do not infuse SYLVANT concomitantly in the same intravenous line with other agents.
6. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Ltd
P O Box 62027
Sylvia Park
AUCKLAND 1644
Telephone: +64 9 918 5100

9. DATE OF FIRST APPROVAL

2 July 2015

10. DATE OF REVISION OF THE TEXT

18 December 2023

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
4.4	Addition of pancreatitis reports with other IL6 inhibitors.
4.8	Addition of 'Reporting of suspected adverse reactions'.