PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSYLVANT®

siltuximab for injection

Lyophilized powder for injection, for intravenous infusion
100 mg/vial and 400 mg/vial

Anti-Interleukin-6 monoclonal antibody

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PrSYLVANT®

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Lyophilized powder for injection, for intravenous infusion
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Interleukin-6 monoclonal antibody

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Sterile lyophilized powder for injection / 100 mg and 400 mg per vial	None *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

SYLVANT® (siltuximab) is indicated for:
- The treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8)-negative.

Pediatrics:
The safety and efficacy of SYLVANT® have not been studied in pediatric patients.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Anaphylaxis
One case of anaphylaxis (1/82 [1.2%], grade 3) has occurred during infusion with SYLVANT® in MCD studies. Appropriate personnel and medication should be available during infusion to treat anaphylaxis.

Treatment with SYLVANT® should be immediately and permanently discontinued in patients who have severe infusion-related hypersensitivity reactions (e.g. anaphylaxis) (see **WARNINGS AND PRECAUTIONS, Allergic and Infusion Reactions, and ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**).

Serious Infections
Infections, including localized infections, should be treated prior to administration of SYLVANT®. Serious infections including pneumonia and sepsis were observed during clinical studies.

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. Treat infections promptly, and do not administer further SYLVANT® until the infection resolves.

Allergic and infusion reactions

Anaphylaxis has occurred during infusion with SYLVANT® (*see Anaphylaxis above).*

In the MCD 2001clinical study, SYLVANT® was associated with an infusion-related reaction or hypersensitivity reaction in 7.5% of patients treated with SYLVANT® monotherapy vs. 0 % in the placebo group.

During IV infusion of SYLVANT®, mild to moderate infusion reactions may improve following slowing of or stopping the infusion. In clinical trials of siltuximab monotherapy dosed at 11 mg/kg, 3.7% of patients in clinical trials required dose delay or interruption due to an infusion-related reaction.

The most common infusion related reactions reported in siltuximab-treated subjects (≥2 subjects) were pruritus, erythema, chest pain, and nausea. Upon resolution of the reaction, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, acetaminophen, and corticosteroids may be considered. In the MCD2001 clinical study, 5.7% of subjects treated with siltuximab were administered antihistamines in association with an infusion-related reaction versus 0% in the placebo group, and 3.8% were administered corticosteroids in association with an infusion-related reaction versus 0% in the placebo group. For patients who do not tolerate the infusion following these interventions, SYLVANT® should be discontinued.

Carcinogenesis and Mutagenesis
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.

Cardiovascular
Hypertension has been reported as an adverse event in siltuximab clinical trials in MCD patients (13.4% vs 3.8% in the placebo group; 7.3% Grade 3 or 4 vs 0% in the placebo group).

Hypotension (grade 3 or higher) has been reported as an adverse event in clinical trials in MCD patients (1.2% vs 0% in the placebo group).

Endocrine and Metabolism
In patients treated with SYLVANT®, elevations in triglycerides (13.4% vs 0% in the placebo group) and cholesterol (lipid parameters) (8.5% vs 0% in the placebo group) were reported as adverse events. In the MCD 2001 clinical study, 5.7% of SYLVANT®-treated subjects were administered a lipid-modifying agent in association with an adverse event of hypertriglyceridemia of hypercholesterolemia (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**). Patients should be managed according to current clinical guidelines for management of hyperlipidemia.

In MCD studies, hyperuricemia was reported in 14.6% vs 0% in the placebo group (grade 3 or higher: 3.7% vs. 0). An increase in uric acid levels was reported in MCD studies (13.4% grade 4 vs 15.4% grade 4 in the placebo group).

Gastrointestinal
Gastrointestinal (GI) perforation has been reported in siltuximab clinical trials (0.75%) although not in MCD trials. Use with caution in patients who may be at increased risk for GI perforation. Advise patients of symptoms suggestive of GI perforation. Promptly evaluate patients presenting with symptoms that may be associated or suggestive of GI perforation.

Hematologic
Polycythemia was reported as a serious adverse event in siltuximab clinical trials in MCD patients (1.2%).

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.

Immune
In MCD clinical trials, grade 3 or grade 4 neutropenia was reported as an adverse event in 3/82 [3.7%] of siltuximab-treated patients versus 1/26 [3.8%] in placebo-treated patients.

Live, attenuated vaccines should not be given concurrently or within 4 weeks before initiating SYLVANT® because clinical safety has not been established.

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® did not bind to virally produced IL-6 in a nonclinical study. Patients should be tested to confirm they are not HIV or HHV-8 positive before treatment.

Renal impairment
Renal impairment was reported in 12.2% vs 0% in the placebo group (2.4% grade 3 or higher vs 0% in the placebo group).

Special Populations

Pregnant Women: There are no data from the use of SYLVANT® in pregnant women. No maternal or fetal toxicity was observed in cynomolgus monkeys after intravenous administration of siltuximab (see ***Product Monograph* Part II*:* TOXICOLOGY, Reproductive and Developmental Toxicity**). However, as with other immunoglobulin G antibodies, siltuximab crosses the placenta as observed in studies in monkeys.

It is not known whether siltuximab can cause fetal 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 for 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 **DRUG INTERACTIONS**). As siltuximab crosses the placenta resulting in fetal exposure, 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.

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 (see ***Product Monograph* Part II*:* TOXICOLOGY, *Reproductive and Developmental Toxicity***).

Nursing Women: It is not known whether siltuximab or its metabolites are excreted in human milk. Serum globulin levels were decreased in pregnant animals (GD 34 through lactation day 30) and in the offspring (lactation days 30-120) at both 10 mg and 50 mg/kg weekly IV doses.

Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SYLVANT®, including increased risk of infection, women should not breast-feed their infants while taking 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.

No impact on male fertility was observed in animal studies at doses up to 100 mg/kg. Male patients and their female partners of childbearing potential must use effective contraceptive methods during treatment and for 3 months after all treatment has ended.

Pediatrics (< 18 years of age): The safety and efficacy of SYLVANT® have not been studied in pediatric patients.

Geriatrics (> 65 years of age): Clinical studies did not include sufficient numbers of patients aged 65 and over (7%) to determine the effect of age on efficacy in the MCD population. No major age-related differences in pharmacokinetic (PK) or in safety profile were observed in clinical studies, but greater sensitivity of some older individuals cannot be ruled out (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions, Geriatrics**).

Monitoring and Laboratory Tests
Hematology laboratory tests (absolute neutrophil count, platelet count and hemoglobin) should be performed prior to each dose of SYLVANT® therapy for the first 12 months and every 3 dosing cycles thereafter (see **DOSAGE AND ADMINISTRATION**). The prescriber should consider delaying treatment if the treatment criteria outlined in **Table 1.5**, **DOSAGE AND ADMINISTRATION** are not met, before administering SYLVANT®.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Data from all patients treated with SYLVANT® monotherapy (n=365) at various doses form the overall basis of the safety evaluation.

The most frequent ADRs (> 20% of patients) during treatment with SYLVANT® in the MCD clinical trials were upper respiratory tract infection (37.8%), pruritus (29.3%), and maculo-papular rash (23.2%).

The most serious ADR associated with the use of SYLVANT® was anaphylactic reaction (1.2%).

Adverse events leading to dose delay or interruption in MCD studies were reported in 32.9% (27/82) of siltuximab-treated subjects vs 19.2% (5/26) in the placebo group. Adverse events leading to discontinuation were reported in 18.3% (15/82) of siltuximab-treated subjects vs 38.5% (10/26) in the placebo group.

Infections
In the MCD clinical studies, SYLVANT® was associated with upper respiratory tract infections in 37.8% of patients versus 15.4% of placebo-treated patients. Nasopharyngitis occurred in 13.4% of patients treated with siltuximab monotherapy, compared to 3.8% of placebo-treated patients.

Serious infections included pneumonia and sepsis.

Lipid parameters
In the MCD clinical studies, SYLVANT® was associated with a higher incidence of hypertriglyceridemia compared with placebo-treated patients (13.4% versus 0%, respectively).

Infusion related reactions and hypersensitivity
In the MCD 2001clinical study, SYLVANT® was associated with an infusion-related reaction or hypersensitivity reaction in 7.5% of patients treated with SYLVANT® monotherapy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

- In Study 1, a randomized placebo controlled Phase 2 study in MCD, 53 patients were randomized to the SYLVANT® treatment arm and treated at the recommended dose, 11/mg/kg, every 3 weeks and 26 patients were randomized to the placebo arm. Of the 26 placebo-treated patients, 13 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 dose of 11 mg/kg every 3 weeks.

Table 1.1 reflects the frequencies of identified adverse drug reactions (ADRs) in Study 1.

Table 1.1: Adverse drug reactions in SYLVANT®-treated patients in study CNTO328MCD2001

	Placebo + BSC[b] N=26		SYLVANT® + BSC[a] N=53	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Blood and lymphatic system disorders				
Neutropenia	7.7%	3.8%	13.6%	4.5%
Thrombocytopenia	3.8%	3.8%	13.6%	3.0%
Gastrointestinal disorders				
Abdominal pain	3.8%	3.8%	13.6%	0.0%
General disorders and administration site conditions				
Localised oedema	3.8%	0.0%	18.2%	3.0%
Immune system disorders				
Anaphylactic reaction	0.0%	0.0%	1.5%	1.5%
Infections and infestations				
Nasopharyngitis	3.8%	0.0%	12.1%	0.0%
Upper respiratory tract infection	15.4%	3.8%	31.8%	0.0%
Investigations				
Weight increased	0.0%	0.0%	16.7%	3.0%
Metabolism and nutrition disorders				
Hypertriglyceridaemia	0.0%	0.0%	10.6%	3.0%
Renal and urinary disorders				
Renal impairment	0.0%	0.0%	10.6%	3.0%
Skin and subcutaneous tissue disorders				

Table 1.1: Adverse drug reactions in SYLVANT®-treated patients in study CNTO328MCD2001

	Placebo + BSC[b] N=26		SYLVANT® + BSC[a] N=53	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Pruritus	11.5%	0.0%	36.4%	0.0%
Rash maculo-papular	11.5%	0.0%	28.8%	1.5%
Vascular disorders				
Hypertension	3.8%	0.0%	10.6%	6.1%

[a]All patients with CD treated with SYLVANT® in study CNTO328MCD2001at recommended dose of 11 mg/kg every 3 weeks [including crossover patients (N=66)], BSC=Best Supportive Care
[b]All patients with CD treated with placebo (N=26) in study CNTO328MCD2001.

Treatment-emergent adverse events reported in ≥3% of patients in the 82 MCD patients (Study 1 and Study 2) treated at the recommended dose of 11 mg/kg every 3 weeks are presented in Table 1.2.

Table 1.2: Treatment-emergent adverse events (≥ 3%) in integrated MCD studies at target dose

		Siltuximab
	Placebo	Total Target Dose[a]
Subjects in safety population	26	82
Total number of subjects with adverse events	25 (96.2%)	82 (100.0%)
System organ class/preferred term		
Gastrointestinal disorders	13 (50.0%)	58 (70.7%)
Diarrhoea	5 (19.2%)	21 (25.6%)
Vomiting	2 (7.7%)	15 (18.3%)
Abdominal pain	1 (3.8%)	13 (15.9%)
Nausea	5 (19.2%)	13 (15.9%)
Constipation	1 (3.8%)	10 (12.2%)
Abdominal pain upper	2 (7.7%)	6 (7.3%)
Abdominal distension	0	5 (6.1%)
Aphthous stomatitis	0	5 (6.1%)
Ascites	2 (7.7%)	4 (4.9%)
Dyspepsia	3 (11.5%)	4 (4.9%)
Gastrooesophageal reflux disease	0	4 (4.9%)
Abdominal pain lower	1 (3.8%)	3 (3.7%)
Stomatitis	0	3 (3.7%)
Dysphagia	1 (3.8%)	2 (2.4%)
Tongue ulceration	1 (3.8%)	2 (2.4%)
Tongue coated	1 (3.8%)	1 (1.2%)
Coeliac disease	1 (3.8%)	0

Table 1.2: Treatment-emergent adverse events (≥ 3%) in integrated MCD studies at target dose

	Placebo	Siltuximab Total Target Dose[a]
Oesophagitis	1 (3.8%)	0
Regurgitation	1 (3.8%)	0
Infections and infestations	9 (34.6%)	56 (68.3%)
Upper respiratory tract infection	4 (15.4%)	31 (37.8%)
Nasopharyngitis	1 (3.8%)	11 (13.4%)
Urinary tract infection	0	7 (8.5%)
Rash pustular	1 (3.8%)	6 (7.3%)
Gastroenteritis	2 (7.7%)	5 (6.1%)
Sinusitis	1 (3.8%)	4 (4.9%)
Bronchitis	0	3 (3.7%)
Cellulitis	0	3 (3.7%)
Herpes zoster	1 (3.8%)	2 (2.4%)
Pneumonia	1 (3.8%)	2 (2.4%)
Bronchopneumonia	1 (3.8%)	1 (1.2%)
Folliculitis	2 (7.7%)	1 (1.2%)
Tooth abscess	1 (3.8%)	1 (1.2%)
Lung infection	1 (3.8%)	0
Oral candidiasis	1 (3.8%)	0
Skin and subcutaneous tissue disorders	11 (42.3%)	51 (62.2%)
Pruritus	3 (11.5%)	24 (29.3%)
Rash maculo-papular	3 (11.5%)	19 (23.2%)
Hyperhidrosis	4 (15.4%)	15 (18.3%)
Night sweats	3 (11.5%)	14 (17.1%)
Rash	1 (3.8%)	12 (14.6%)
Dry skin	0	6 (7.3%)
Eczema	0	6 (7.3%)
Skin hyperpigmentation	0	5 (6.1%)
Dermatitis acneiform	2 (7.7%)	4 (4.9%)
Rash pruritic	0	4 (4.9%)
Erythema	1 (3.8%)	3 (3.7%)
Skin induration	1 (3.8%)	3 (3.7%)
Blister	1 (3.8%)	1 (1.2%)
Skin mass	1 (3.8%)	1 (1.2%)
General disorders and administration site conditions	17 (65.4%)	50 (61.0%)
Fatigue	10 (38.5%)	25 (30.5%)
Oedema peripheral	6 (23.1%)	21 (25.6%)
Malaise	5 (19.2%)	19 (23.2%)
Localised oedema	1 (3.8%)	12 (14.6%)
Generalised oedema	2 (7.7%)	10 (12.2%)
Pyrexia	2 (7.7%)	9 (11.0%)

Table 1.2: Treatment-emergent adverse events (≥ 3%) in integrated MCD studies at target dose

		Siltuximab
	Placebo	Total Target Dose[a]
Face oedema	1 (3.8%)	6 (7.3%)
Pain	1 (3.8%)	6 (7.3%)
Oedema	0	4 (4.9%)
Asthenia	1 (3.8%)	2 (2.4%)
Chest pain	2 (7.7%)	1 (1.2%)
Influenza like illness	1 (3.8%)	1 (1.2%)
Metabolism and nutrition disorders	10 (38.5%)	44 (53.7%)
Decreased appetite	4 (15.4%)	13 (15.9%)
Hyperuricaemia	0	12 (14.6%)
Hypertriglyceridaemia	0	11 (13.4%)
Hypokalaemia	2 (7.7%)	11 (13.4%)
Hypercholesterolaemia	0	7 (8.5%)
Hypocalcaemia	1 (3.8%)	6 (7.3%)
Enzyme abnormality	2 (7.7%)	4 (4.9%)
Hyperglycaemia	1 (3.8%)	4 (4.9%)
Hyperkalaemia	0	3 (3.7%)
Hypoalbuminaemia	1 (3.8%)	3 (3.7%)
Hypomagnesaemia	0	3 (3.7%)
Hypoglycaemia	1 (3.8%)	2 (2.4%)
Hyponatraemia	1 (3.8%)	2 (2.4%)
Respiratory, thoracic and mediastinal disorders	14 (53.8%)	40 (48.8%)
Dyspnoea	9 (34.6%)	19 (23.2%)
Cough	6 (23.1%)	12 (14.6%)
Oropharyngeal pain	1 (3.8%)	8 (9.8%)
Pleural effusion	3 (11.5%)	7 (8.5%)
Productive cough	1 (3.8%)	3 (3.7%)
Rhinitis allergic	0	3 (3.7%)
Sleep apnoea syndrome	1 (3.8%)	0
Musculoskeletal and connective tissue disorders	8 (30.8%)	33 (40.2%)
Arthralgia	2 (7.7%)	10 (12.2%)
Back pain	3 (11.5%)	9 (11.0%)
Muscular weakness	0	5 (6.1%)
Musculoskeletal pain	1 (3.8%)	5 (6.1%)
Pain in extremity	0	5 (6.1%)
Muscle spasms	2 (7.7%)	4 (4.9%)
Myalgia	1 (3.8%)	4 (4.9%)
Arthritis	1 (3.8%)	0
Chondropathy	1 (3.8%)	0
Osteoporosis	1 (3.8%)	0

Table 1.2: Treatment-emergent adverse events (≥ 3%) in integrated MCD studies at target dose

		Siltuximab
	Placebo	Total Target Dose[a]
Pain in jaw	1 (3.8%)	0
Nervous system disorders	8 (30.8%)	32 (39.0%)
Peripheral sensory neuropathy	5 (19.2%)	18 (22.0%)
Headache	1 (3.8%)	11 (13.4%)
Peripheral motor neuropathy	2 (7.7%)	8 (9.8%)
Dizziness	2 (7.7%)	7 (8.5%)
Syncope	0	3 (3.7%)
Somnolence	1 (3.8%)	2 (2.4%)
Blood and lymphatic system disorders	8 (30.8%)	31 (37.8%)
Thrombocytopenia	1 (3.8%)	11 (13.4%)
Anaemia	4 (15.4%)	10 (12.2%)
Neutropenia	2 (7.7%)	9 (11.0%)
Leukopenia	1 (3.8%)	6 (7.3%)
Lymphopenia	2 (7.7%)	2 (2.4%)
Lymph node pain	1 (3.8%)	1 (1.2%)
Lymphocytic infiltration	1 (3.8%)	0
Investigations	7 (26.9%)	31 (37.8%)
Weight increased	0	12 (14.6%)
Weight decreased	4 (15.4%)	6 (7.3%)
Serum ferritin decreased	0	4 (4.9%)
Blood albumin decreased	2 (7.7%)	3 (3.7%)
Haemoglobin increased	0	3 (3.7%)
Protein total increased	0	3 (3.7%)
Blood iron decreased	1 (3.8%)	1 (1.2%)
Protein urine present	1 (3.8%)	1 (1.2%)
Blood thyroid stimulating hormone increased	1 (3.8%)	0
Iron binding capacity total decreased	1 (3.8%)	0
Iron binding capacity unsaturated decreased	1 (3.8%)	0
Platelet count increased	1 (3.8%)	0
Vitamin B12 decreased	1 (3.8%)	0
Vascular disorders	1 (3.8%)	19 (23.2%)
Hypertension	1 (3.8%)	11 (13.4%)
Flushing	0	6 (7.3%)
Hypotension	0	3 (3.7%)
Renal and urinary disorders	2 (7.7%)	18 (22.0%)
Renal impairment	0	10 (12.2%)
Azotaemia	1 (3.8%)	5 (6.1%)
Pollakiuria	1 (3.8%)	4 (4.9%)

Table 1.2: Treatment-emergent adverse events (≥ 3%) in integrated MCD studies at target dose

		Siltuximab
	Placebo	Total Target Dose[a]
Bladder pain	1 (3.8%)	0
Eye disorders	4 (15.4%)	17 (20.7%)
Vision blurred	0	5 (6.1%)
Periorbital oedema	1 (3.8%)	4 (4.9%)
Conjunctivitis	2 (7.7%)	1 (1.2%)
Eye pruritus	1 (3.8%)	0
Orbital pseudotumour	1 (3.8%)	0
Injury, poisoning and procedural complications	2 (7.7%)	15 (18.3%)
Fall	1 (3.8%)	2 (2.4%)
Ligament sprain	1 (3.8%)	1 (1.2%)
Hepatobiliary disorders	2 (7.7%)	12 (14.6%)
Hepatic function abnormal	2 (7.7%)	8 (9.8%)
Hyperbilirubinaemia	0	4 (4.9%)
Psychiatric disorders	3 (11.5%)	12 (14.6%)
Insomnia	2 (7.7%)	5 (6.1%)
Depression	1 (3.8%)	3 (3.7%)
Reproductive system and breast disorders	2 (7.7%)	12 (14.6%)
Oedema genital	1 (3.8%)	3 (3.7%)
Pelvic pain	1 (3.8%)	1 (1.2%)
Cardiac disorders	1 (3.8%)	10 (12.2%)
Cardiac failure congestive	1 (3.8%)	0
Immune system disorders	1 (3.8%)	9 (11.0%)
Seasonal allergy	1 (3.8%)	3 (3.7%)
Ear and labyrinth disorders	1 (3.8%)	8 (9.8%)
Ear pain	0	3 (3.7%)
Tinnitus	1 (3.8%)	1 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (23.1%)	6 (7.3%)
Tumour pain	4 (15.4%)	5 (6.1%)
Myelodysplastic syndrome	1 (3.8%)	0
T-cell lymphoma	1 (3.8%)	0
Endocrine disorders	1 (3.8%)	1 (1.2%)
Cushingoid	1 (3.8%)	0

[a] Includes subjects who crossed over from placebo to siltuximab in Study CNTO328MCD2001.
Adverse events were coded using MedDRA version 15.1.

Abnormal Hematologic Findings
Abnormal hematology parameters (Grade 3 and Grade 4) are provided in Table 1.3.

Table 1.3: Summary of hematology worst CTC grade ≥ 3 at post-baseline; safety population (Integrated MCD Studies)

	Placebo	Siltuximab
Subjects in safety population	26	82
Hemoglobin (decrease)	3 (11.5%)	2 (2.4%)
Polycythemia	0	1 (1. 2%)
Lymphocytes (decrease)	2 (7.7%)	10 (12.2%)
Neutrophils (decrease)	1 (3.8%)	6 (7.3%)
Platelet (decrease)	1 (3.8%)	4 (4.9%)
WBC (decrease)	0	1 (1.2%)

Studies with siltuximab monotherapy at 11 mg/kg
Treatment-emergent adverse events of Grade 3 or higher intensity were integrated from studies of siltuximab monotherapy administered at the target dose of 11 mg/kg in patients with various disease types (including MCD, malignant solid tumours, metastatic renal cell carcinoma, myelodysplastic syndrome, and smoldering multiple myeloma). In this safety population, Grade 3 or higher adverse events with at least a 5% incidence in siltuximab-treated subjects included: thrombocytopenia (5.9%), fatigue (5.9%), dyspnea (5.9%) and hypertension (7.8%) (Table 1.4).

Table 1.4: Treatment-emergent adverse events (≥ 5%) with Grade 3 or higher intensity in siltuximab monotherapy studies conducted at the target dose of 11 mg/kg[a].

	SYLVANT® + BSC at 11 mg/kg target dose N=102	Placebo + BSC N=52
Total number of subjects with adverse events	57 (55.9%)	22 (42.3%)
Blood and lymphatic system disorders		
Neutropenia	9 (8.8%)	3 (5.8%)
Anaemia	3 (2.9%)	3 (5.8%)
Thrombocytopenia	6 (5.9%)	1 (1.9%)
General disorders and administration site conditions		
Fatigue	6 (5.9%)	1 (1.9%)
Infections and infestations		
Pneumonia	1 (1.0%)	1 (1.9%)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	6 (5.9%)	1 (1.9%)
Vascular disorders		
Hypertension	8 (7.8%)	0
Hepatobiliary disorders		
Hepatic function abnormal	1 (1.0%)	1 (1.9%)

[a] Monotherapy studies in MCD, malignant solid tumours, metastatic renal cell carcinoma, myelodysplastic syndrome, and smoldering multiple myeloma.
BSC=Best Supportive Care.

Post-Market Adverse Drug Reactions
Not available.

DRUG INTERACTIONS

Overview
No formal drug-drug interaction studies have been conducted with SYLVANT®.

Drug-Drug Interactions
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 normalize. 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, atorvastatin).

No physical biochemical compatibility studies have been conducted to evaluate the co-administration of SYLVANT® with other agents.

Drug-Food Interactions
No formal drug-food interaction studies have been conducted with siltuximab.

Drug-Herb Interactions
No formal drug-food interaction studies have been conducted with siltuximab.

Drug-Laboratory Interactions
No formal drug-laboratory studies have been conducted with siltuximab.

Drug-Lifestyle Interactions
No formal drug-lifestyle interaction studies have been conducted with siltuximab.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Intravenous infusion (IV) of SYLVANT® should be administered by qualified healthcare professionals. Comprehensive instructions for the intravenous infusion of SYLVANT® are given in "**Administration**".

- The SYLVANT® therapy should be withheld if the patient has a severe infection or any severe non-hematological 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.
- SYLVANT® did not bind to virally produced IL-6 in a nonclinical study. Patients should be tested to confirm they are not HIV or HHV-8 positive before treatment.

Recommended Dose and Dosage Adjustment
SYLVANT® 11 mg/kg is given over 1 hour as an intravenous infusion administered every 3 weeks until treatment failure.

Hematology 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 1.5 are not met, before administering SYLVANT®. Dose reduction is not recommended.

Table 1.5 Treatment criteria

Laboratory Parameter	Requirements Before First SYLVANT® Administration	Retreatment Criteria
Absolute Neutrophil Count	$\geq 1.0 \times 10^9$/L	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 75 \times 10^9$/L	$\geq 50 \times 10^9$/L
Hemoglobin[a]	< 170 g/L	< 170 g/L

[a]SYLVANT® may increase hemoglobin levels in MCD patients

Missed Dose
If the patient misses a dose of SYLVANT®, the patient should be directed to make another appointment to be administered SYLVANT® as soon as possible.

Administration
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 (38mm). 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 the 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.

Reconstitution:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
100 mg	5.2 mL of single use sterile water for injection	5 mL	20 mg/mL
400 mg	20.0 mL of single use sterile water for injection	20 mL	20 mg/mL

Gently swirl (**do not shake or swirl vigorously**) the reconstituted vials to aid the dissolution of the lyophilized powder. Do not remove the contents until all of the solids have been completely dissolved. The lyophilized powder should dissolve in less than 60 minutes. Inspect the vials for particulate matter and discoloration prior to dose preparation. Do not use the vials 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% in Water, by withdrawing a volume equal to the volume of reconstituted SYLVANT® from the Dextrose 5% in Water, 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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Repeated dosing of 15 mg/kg every 3 weeks has been administered without additional adverse reactions.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Siltuximab is a human-mouse chimeric monoclonal antibody that forms high affinity, stable complexes with soluble bioactive forms of human interleukin-6 (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 signaling complex with gp130 on the cell surface. IL-6 is a pleiotropic pro-inflammatory 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 anemia and cachexia and has been hypothesized to play a central role in driving plasma cell proliferation and systemic manifestations in patients with CD.

Pharmacodynamics

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.

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 1 of 411 evaluable patients (having 1 or more immunogenicity samples obtained after their first siltuximab administration) tested positive for anti-siltuximab antibodies. Further immunogenicity analyses of the single positive sample revealed a low titer of anti-siltuximab antibodies with non-neutralizing capabilities. No evidence of altered toxicity profile was identified in the patient who developed antibodies to siltuximab.

Pharmacokinetics
Following the first administration of siltuximab ranging from 0.9 to 15 mg/kg, the area under the concentration-time curve (AUC) and maximal serum concentration (Cmax) increased in an approximately dose-proportional manner and clearance (CL) was independent of dose. During administration of siltuximab, serum concentrations increase through the end of infusion and then decline in a biphasic manner with an initial more rapid decrease in concentration followed by a slower elimination phase. 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 time-invariant, and systemic accumulation was moderate (accumulation index of 1.7). In subjects with MCD, the mean CL after the first dose was higher (6.14 ± 2.96 mL/kg/day), however, consistent with the previously reported 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.

Absorption: Absorption data are not available since all studies administered siltuximab as an IV infusion.

Distribution: Siltuximab is primarily localized to the circulatory system with limited extravascular tissue distribution.

Metabolism: As an IgG1κ mAb, siltuximab is presumably metabolized in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination.

Excretion: No formal studies have been conducted.

Special Populations and Conditions

Pediatrics: The safety and efficacy of siltuximab have not been established in pediatric patients.

Geriatrics: Clinical studies did not include sufficient numbers of patients aged 65 and over (7%) to determine the effect of age on efficacy in the MCD population. No major age-related differences in pharmacokinetic (PK) or in safety profile were observed in clinical studies, but greater sensitivity of some older individuals cannot be ruled out.

Gender: No clinical effect on the clearance of siltuximab was observed in population pharmacokinetic analyses.

Ethnic origin: No clinical effect on the clearance of siltuximab was observed in population pharmacokinetic analyses.

Hepatic Insufficiency: No formal studies of siltuximab in subjects with hepatic impairment have been conducted. For subjects with baseline alanine transaminase ranging from 0.1 to 3.7 times the upper limit of normal, baseline bilirubin ranging from 1.71 to 42.75 mg/dL, baseline albumin ranging from 1.5 to 5.8 g/dL, there was no meaningful effect on siltuximab PK.

Renal Insufficiency: No formal studies of siltuximab in subjects with renal impairment have been conducted. For subjects with baseline calculated creatinine clearance of 12 mL/min or greater, there was no meaningful effect on siltuximab PK. In addition, there were no significant differences in PK for subjects with normal, Stage 2, and Stage 3 impaired renal function.

Genetic Polymorphism: No formal studies have been conducted.

STORAGE AND STABILITY

SYLVANT® must be refrigerated at 2ºC to 8ºC. Do not use SYLVANT® beyond the expiration date located on the carton and the vial. This product contains no preservative. Do not freeze. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

Keep out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each SYLVANT® 8 mL or 30 mL vial is individually packaged in a carton. SYLVANT® is supplied in a carton containing 1 vial.

For 100 mg presentation:

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

For 400 mg presentation:

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

Nonmedicinal ingredients include: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate-80 and sucrose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: siltuximab

Chemical name: Chimeric (human-murine) IgG1κ mAb

Physicochemical properties: Siltuximab is a chimeric (human-murine) IgG1κ mAb that specifically binds human IL-6 with high affinity and prevents its interaction with the IL-6 receptor, glycoprotein (GP) 80. The chimeric antibody contains the variable region of a murine anti human IL-6 mAb and the constant region from a human immunoglobulin gamma (IgG) 1 molecule.

A lyophilized formulation contains siltuximab at pH 4.9 to 5.6 after reconstitution of the lyophile.

CLINICAL TRIALS

Study demographics and trial design

Table 2.1 - Summary of patient demographics for clinical trials in Multicentric Castleman's disease

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Race	Gender
Study 1: CNTO328-MCD2001	Randomized, double-blind, placebo-controlled, Phase 2 study	11 mg/kg every 3 weeks; Intravenous infusion; Mean treatment duration, siltuximab: 424 days (SD 272)	N=79	45.5 (20; 78) years	48% Asian 39% Caucasian	Male: 65.8% Female: 34.2%
Study 2: C0328T03	Open-label, nonrandomized, dose-finding Phase 1 study	2.8 – 11 mg/kg, weekly to every 3 weeks; Intravenous infusion; Duration: 3 – 7 administrations	N=67 Patients with MCD treated with 11 mg/kg: 16 (24%)	54.4 (18 – 80) years	79.1% Caucasian 14.9% Black 6% Asian	Male: 51.4% Female: 48.6%

<u>Study 1</u>

A Phase 2, multinational, randomized (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), discontinuation of treatment, withdrawal from the study, unacceptable toxicity, or until 48 weeks after the last subject started study treatment, whichever occurred earlier. A total of 79 patients with symptomatic MCD were randomized and treated. Table 2.2 presents patient demographic and baseline characteristics for Study 1.

Table 2.2: Patient demographics and baseline characteristics

	SYLVANT® + BSC N=53	**Placebo + BSC N=26**
Median age, years (range)	47.0 (20; 74)	48.0 (27; 78)
Sex, n (%)		
Male	30 (56.6)	22 (84.6)
Female	23 (43.4%)	4 (15.4%)
Race, n (%)		
White	19 (35.8)	12 (46.2%)
Black	3 (5.7%)	0
Asian	27 (50.9)	11 (42.3)
Median weight, kg (range)	67.0 (42.0; 111.4)	70.2 (47.5; 121.2)
Histological subtype by central pathology, n (%)	Hyaline vascular: 18 (34.0) Plasmacytic: 13 (24.5%) Mixed: 22 (41.5%)	Hyaline vascular: 8 (30.8) Plasmacytic: 5 (19.2%) Mixed: 13 (50.0%)
MCD-related signs and symptoms at baseline, n (%)		
6-10 symptoms	16 (30.2)	15 (57.7)
>10 symptoms	6 (11.3)	4 (15.4)
MCD-related signs and symptoms by NCI-CTCAE grade, n (%)		
Grade 1	22 (41.5)	7 (26.9%)
Grade 2	21 (39.6)	14 (53.8)
Grade 3	10 (18.9)	4 (15.4)
Grade 4	0	1 (3.8)
Number of prior systemic therapies, n (%)		
0	24 (45.3)	9 (34.6)
1	18 (34.0)	8 (30.8)
2	4 (7.5)	4 (15.4)
3	4 (7.5)	1 (3.8)
>3	3 (5.7)	4 (15.4)
Corticosteroid use at randomization, n (%)		
Yes	16 (30.2)	8 (30.8)
No	37 (69.8)	18 (69.2)

The primary endpoint of the study was durable tumor and symptomatic response, defined as tumour response (PR and CR based on modified International Working Group response criteria for malignant lymphoma) assessed by independent review and complete resolution or

stabilization of prospectively collected MCD symptoms. Thirty-four MCD related signs and symptoms prospectively identified were collected and graded according to the NCI-CTCAE v 4, by investigators. A durable response was defined as tumor and symptomatic response that persisted for a minimum of 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).

Key efficacy results from Study 1 are summarized in Table 2.3.

Table 2.3: Efficacy endpoints from Study 1

Efficacy Endpoints	**SYLVANT® +BSC**	**Placebo+BSC**	**P-value[a]**
Primary Efficacy Endpoint			
Durable tumour and 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%)	
Median Time to treatment failure	Not reached	134 days	

[a] Adjusted for corticosteroid use at randomization
[b] N/A="Not applicable", there were no responders in the placebo arm, therefore, duration is not applicable

Hemoglobin response was defined as a change from baseline of ≥ 15g/L at week 13. In the response evaluable population, 61.3% (19/31) of siltuximab-treated subjects had a hemoglobin increase of at least 15 g/L at week 13, versus 0% in the placebo group.

One-year survival rate was 100% in the SYLVANT® arm and 92% in the placebo arm. Overall survival data was not mature at the time of analysis.

Subgroup analyses:
The primary endpoints on various subgroups including age (< 65 years and ≥ 65 years); race (White and Non-White); region (North America, Europe, 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 favored the SYLVANT® arm except no patients with hyaline vascular histology demonstrated a durable tumor and symptomatic response. However, a consistent treatment effect favouring SYLVANT®-treated patients in the secondary endpoints of best tumour response and median time to treatment failure was shown in the hyaline vascular subgroup.

Study 2
In addition to Study 1, data are available in patients with Castleman's disease from a single-arm Phase 1 study (Study 2). In this study, 16 out of 37 patients with MCD were treated with 11 mg/kg every 3 weeks. In these 16 patients with MCD treated with 11 mg/kg every 3 weeks for a median of 92 weeks (range 8.1, 252.3), overall tumour response rate by independent review was

43.8% with 6.3% complete response. Eleven of these patients have moved into a long-term extension study and have been treated for a median duration of 68 months (range 40.9, 85.1). All tumour responses were durable for > 18 weeks.

DETAILED PHARMACOLOGY

Clinical Pharmacokinetics

A population pharmacokinetic (PK) analysis was performed and a two-compartment model described the time course of serum siltuximab concentration following multiple intravenous (IV) administrations in 378 subjects with multicentric Castleman's disease (MCD), Castleman's disease (CD), renal cell carcinoma (RCC), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), prostate cancer, ovarian cancer, and smoldering multiple myeloma (SMM) who received single-agent siltuximab at doses ranging from 0.9 to 15 mg/kg.

Body weight had a statistically significant impact on all siltuximab PK parameters (CL, VC, Q, and VP) and was the only clinically relevant covariate in the model. This supports a strategy of body weight-based dosing of siltuximab.

No formal studies of siltuximab in subjects with renal impairment have been conducted. In the population PK analysis, baseline CRCL was used as an indicator for renal function. Creatinine clearance was not found to be significant and therefore does not warrant dose adjustment. Therefore, CRCL at baseline was not assumed to have a clinically relevant effect on siltuximab PK in subjects with calculated CRCL values of 12 mL/min or greater.

No formal studies of siltuximab in subjects with hepatic impairment have been conducted. In the population PK analysis, baseline aspartate aminotransferase (AST), ALT, and ALB were considered in the evaluation of covariates on CL. Since AST and ALT were highly correlated, AST was not assessed as a covariate in the population PK analysis. For subjects with baseline ALT ranging from 0.1 to 3.7 U/L x upper limit of normal (ULN), there was no clinically relevant effect on siltuximab PK. In addition, for subjects with baseline ALB ranging from 1.5 to 5.8 g/dL, and baseline bilirubin ranging from 1.71 to 42.75 mg/dL, there was no clinically relevant effect on siltuximab PK. Clinical relevance of population PK analysis, however, needs to be evaluated concurrently with clinical efficacy and safety data.

No clinical drug interaction studies have been conducted.

Siltuximab PK parameter estimates based on non-compartmental analysis from study CNTO328MCD2001 are presented in table 2.4 below.

Table 2.4: Summary of Siltuximab Pharmacokinetic Parameter Estimates; Subjects Evaluable for Siltuximab PK (Study CNTO328MCD2001)

	Siltuximab + BSC
Subjects evaluable for siltuximab PK[a]	66
$AUC_{(0-t)}$ (μg.day/mL)	
N	66
Mean (SD)	1643.24 (662.488)
Coefficient of variation	40.3%
Geometric mean	1515.92
Median	1452.98
Range	(637.6; 3198.0)
C_{max} (μg/mL)	
N	66
Mean (SD)	250.06 (118.423)
Coefficient of variation	47.4%
Geometric mean	233.47
Median	227.37
Range	(116.1; 1015.1)
AUC_{inf} (μg.day/mL)	
N	60
Mean (SD)	2266.36 (1126.162)
Coefficient of variation	49.7%
Geometric mean	2015.18
Median	1821.99
Range	(726.4; 4827.4)
CL (ml/day/kg)	
N	60
Mean (SD)	6.14 (2.961)
Coefficient of variation	48.2%
Geometric mean	5.48
Median	6.07
Range	(2.3; 15.2)
Serum trough concentrations (ug/mL)[b]	
Cycle 3, Day 1, preinfusion	
N	64
Mean (SD)	53.15 (35.239)
Median	39.62
Range	(6.9; 130.5)
Cycle 6, Day 1, preinfusion	
N	60
Mean (SD)	84.12 (65.631)
Median	68.22
Range	(6.6; 275.0)
Cycle 9, Day 1, preinfusion	
N	51
Mean (SD)	93.95 (66.562)
Median	72.99
Range	(12.9; 257.3)

[a] Subjects evaluable for PK had 1 measurable PK concentration posttreatment record.

[b]Includes subjects who crossed over from placebo to siltuximab treatment.

Clinical Pharmacodynamics

Rapid and sustained suppression of serum C-reactive protein (CRP) (a marker of interleukin-6 [IL-6] bioactivity) levels in subjects with MCD was observed only in the siltuximab group (not in the placebo group) in Study CNTO328MCD2001, which is indicative of in vivo neutralization of IL-6 bioactivity. The CRP suppression in MCD subjects treated with Chinese hamster ovary (CHO)-derived siltuximab in Study MCD2001 was consistent with that observed in MCD subjects treated with Sp2/0-derived siltuximab in an earlier study (C0328T03, Cohort 7b) at the target dose. Subjects with CD treated at the target dose of 11 mg/kg every 3 weeks in Study C0328T03 showed greater decrease of systemic CRP levels compared with those treated with 8.3 mg/kg every 3 weeks, supporting the clinical efficacy observations. Furthermore, the rapid and sustained CRP suppression observed at a dose of 11 mg/kg every 3 weeks was also observed at 15 mg/kg every 3 weeks in subjects with solid tumours. These results indicate that at the target dose of 11 mg/kg every 3 weeks, bioactive IL-6 is adequately suppressed. There was high intersubject variability of systemic IL-6 levels in Study MCD2001 (both complexed and non-complexed), which were not predictive of clinical response (durable tumour and symptomatic response or tumour response). Measurement of serum IL-6 concentrations during treatment cannot be used as a pharmacodynamic marker, as siltuximab-neutralized antibody-IL-6 complexes interfere with current immunological-based IL-6 quantification methods.

TOXICOLOGY

A summary of toxicology studies is provided in Table 2.5.

Table 2.5 Nonclinical toxicology studies

Study Description (Study Number)	Species/Strain or Tissue/Cell Line	Dose/ Concentration/ Vehicle[a]	Route/ Duration of Dosing	Group: Number/Sex	Noteworthy Findings	GLP
Repeat-dose Toxicity						
Repeat-dose toxicity study (T-2009-025)	Mouse	CNTO 345[b] (anti-mouse IL-6 mAb) at 40 and 100 mg/kg	SC or IV weekly or biweekly doses given for 1-month	9 females/group (8 groups total)	No treatment-related adverse effects; all dose routes were well-tolerated and provided sustained systemic exposure.	No
Repeat-dose toxicity study (T-2002-007)	Cynomolgus monkeys	Siltuximab at 0, 9.2 mg/kg, or 46 mg/kg	IV/once weekly x 13 weeks, 2-hour infusions	8/sex/group	Monkeys received significant exposure to siltuximab. Treatment was well tolerated. Statistically significant decrease in IgG titers to KLH at 46 mg/kg, decrease in spleen germinal centers. Slight irritation of injection site vein wall.	Yes
Dose-range finding study (T-2002-008)	Cynomolgus monkeys	Standard clinical regimen of high-dose IL-2 at 600,000, 850,000, or 1,000,000 units/kg	15-minute IV infusion every 8 hours for up to 14 doses each period	2 females/group	1,000,000 units/kg IL-2 identified as the maximum tolerated dose.	No
Combination study with IL-2 (T-2002-010)	Cynomolgus monkeys	Standard clinical regimen of high-dose IL-2 (1,000,000 unit/kg) Siltuximab at 0, 9.2 mg/kg, or 46 mg/kg	IL-2 (3 x daily for 5 days with intervening 9-day rest followed by a second 5-day course of treatment) in combinations with siltuximab (IV/ 13 weekly, 2-hour infusions)	8/sex/group	Toxicities, including mortality, were limited to monkeys receiving IL-2. There were no differences in toxicity between monkeys receiving IL-2 alone and IL-2 in combination with siltuximab.	Yes
Repeat-dose toxicity study (T-2003-010)	Cynomolgus monkeys	Siltuximab at 0, 9.2 mg/kg, or 46 mg/kg	IV/once weekly x26 weeks, 2-hour infusions	5/sex/group	Monkeys received significant exposure to siltuximab. Treatment was well tolerated. Statistically significant decrease in IgG and IgM titers to KLH at 9.2 mg/kg or 46 mg/kg, but no pathologic findings in the lymphoid organs,	Yes

Table 2.5 Nonclinical toxicology studies

Study Description (Study Number)	Species/Strain or Tissue/Cell Line	Dose/ Concentration/ Vehicle[a]	Route/ Duration of Dosing	Group: Number/Sex	Noteworthy Findings	GLP
					including the spleen.	
Reproductive and Developmental Toxicity						
Male fertility (T-2010-033)	Mouse	CNTO 345[b] (anti-mouse IL-6 mAb) at 0, 40, and 100 mg/kg	SC weekly beginning 28 days before cohabitation, through cohabitation (maximum 17 days), and continuing through the day before sacrifice (for a maximum of 7 weeks)	25/group	No effect on male fertility. Paternal NOAEL 100 mg/kg. Male reproductive NOAEL 100 mg/kg.	Yes
Female fertility (T-2010-032)	Mouse	CNTO 345[b] (anti-mouse IL-6 mAb) at 0, 40, and 100 mg/kg	SC weekly beginning 15 days before cohabitation, through cohabitation (maximum 14 days), and on Day 0 and 6 of presumed gestation (up to 5 doses).	25/group	No effect on female fertility. Maternal NOAEL 100 mg/kg. Female reproductive NOAEL 100 mg/kg.	Yes
Embryo-fetal development (T-2005-036)	Cynomolgus monkeys	Siltuximab at 0, 9.2 mg/kg, or 46 mg/kg	IV/once-weekly infusions from GD 20 through Day 118	15 females/group	There were no abortions or embryo-fetal deaths considered related to siltuximab treatment. Normal visceral and skeletal formation.	Yes
Prenatal and postnatal development, including maternal function (T-2010-018)	Cynomolgus monkeys	CNTO 136[c] (humanized IgG1 κ mAb) at 0, 10, and 50 mg/kg	IV weekly from GD 20 – GD 167 (total 22 doses)		There were no abortions or embryo-fetal deaths considered related to treatment with CNTO 136, and CNTO 136 did not impair the normal development of infants exposed in utero, including the ability to mount an immune response against foreign antigen. Maternal and infant NOAEL: 50 mg/kg	Yes

Table 2.5 Nonclinical toxicology studies

Study Description (Study Number)	Species/Strain or Tissue/Cell Line	Dose/ Concentration/ Vehicle[a]	Route/ Duration of Dosing	Group: Number/Sex	Noteworthy Findings	GLP
Other Toxicity						
Tumour immune surveillance (BTTR023)	Mouse/C3H/HeN	CNTO 345[b] (anti-mouse IL-6 mAb) at 0, 0.1, 1, 10, 40, or 100 mg/kg	SC every 2–8 days from Day 1 to Day 22 or 23 (SCC VII tumor cells injected on Day 5)	12/group	No effect on growth of the SCC VII primary tumor. No effect on Qdot® labeled SCC VII cell trafficking. Enhanced metastasis of SCC VII cells to the popliteal lymph node at doses of 1, 10, 40, and 100 mg/kg, (but not 0.1 mg/kg), No effect on immune cell populations in the popliteal lymph node.	No
Tumour immune surveillance (BTTR024)	Mouse/C3H/HeN	CNTO 345[b] (anti-mouse IL-6 mAb) at 0, 10, 40, or 100 mg/kg	SC Days 1 and 4 (SCC VII tumor cells injected on Day 5)	12/group	Decreased SCC VII colonization in the lungs	No
Tumour immune surveillance (BTTR025)	Mouse/C3H/HeN	CNTO 345[b] (anti-mouse IL-6 mAb) at 0, 10, 40, or 100 mg/kg	SC Days 8, 15, and 21 (SCC VII tumor cells injected on Day 5)	12/group	No effect on tumor progression, proliferation index, or angiogenesis.	No
In vitro cross-reactivity study (T-099-001)	Cynomolgus monkeys and human tissue	Siltuximab at 1.25 µg/mL and 12.5 µg/mL	N/A	N/A	Staining was observed in the brain, mononuclear cells in small intestine and tonsils, axons of peripheral nerves, and liver, tonsillar epithelium, and equivocal staining was observed of acinar cells of pancreas and pituicytes in human tissue. Specific staining to central and peripheral nervous tissues and mononuclear cells in the mesenteric lymph node of the cynomolgus monkey. In additional studies, positive staining of tissues was determined to be an artifact of the biotinylation procedure.	No
In vitro cross-reactivity study (T-2002-013)	Human tissue	Siltuximab at 1.25 µg/mL and 12.5 µg/mL	N/A	N/A	Specific reactivity in axons in brain, spinal cord, and peripheral nerves. There was cytoplasmic staining of squamous epithelium in the cornea and thymus.	Yes

Table 2.5 Nonclinical toxicology studies

Study Description (Study Number)	Species/Strain or Tissue/Cell Line	Dose/ Concentration/ Vehicle[a]	Route/ Duration of Dosing	Group: Number/Sex	Noteworthy Findings	GLP
In vitro cross-reactivity study (T-2004-019)	Human tissue	Siltuximab at 1.25 µg/mL and 12.5 µg/mL	N/A	N/A	Positive staining of tissues identified in studies T-099-001 and T-2002-013 were determined to be an artifact of the biotinylation procedure.	Yes
Staining of eye tissues (T-2003-004)	Cynomolgus monkeys	Eye tissue from control group animals Eye tissue from 46 mg/kg siltuximab dose group animals	N/A	N/A	Negative control antibody did not stain eye tissue from control group animals. Siltuximab did not stain (bind) squamous epithelium of the cornea.	Yes

[a] Sterile phosphate-buffered saline (pH 7.4) used as vehicle, unless otherwise specified.
[b] Studies were conducted with CNTO 345, a surrogate anti-mouse IL-6 mAb.
[c] Studies were conducted with CNTO 136, a humanized IgGκ mAb derived from siltuximab that binds to and neutralizes human and cyno. monkey IL-6.

GD = gestation day; Ig = immunoglobulin; IL = interleukin; IV = intravenous; KLH = keyhole limpet hemocyanin; N/A = not applicable; NOAEL = no observed adverse effect level; SC = subcutaneous; SCC = squamous cell carcinoma

REFERENCES

Wong RS, Casper C, Munshi N, et al. A multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with multicentric Castleman's disease. Blood (ASH Annual Meeting Abstracts) 2013. Abstract 505.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrSYLVANT®
pronounced SILL-vant
siltuximab for injection

Read this carefully before you start taking SYLVANT® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about SYLVANT®.

What is SYLVANT® used for?

- SYLVANT® is a prescription medicine that is used to treat adults with multicentric Castleman's disease (MCD) in patients who do not have human immunodeficiency virus (HIV, which causes AIDS) or human herpes virus-8 (HHV-8) infection.
- MCD causes non-cancerous growths (benign tumours) to develop in your lymph nodes ('glands'). You may also feel weak or tired, have fever or sweat a lot, especially at night, have tingling, burning or weakness in your arms or legs, or a loss of appetite.

How does SYLVANT® work?

SYLVANT® blocks the action of a specific protein called "interleukin-6", which can cause inflammation. Blocking this protein helps to reduce the size of your affected lymph.

What are the ingredients in SYLVANT®?

Medicinal ingredients: siltuximab
Non-medicinal ingredients: L-histidine and L-histidine monohydrochloride monohydrate, polysorbate 80, and sucrose.

SYLVANT® comes in the following dosage forms:

Lyophilized (freeze-dried) powder in vials containing 100 mg or 400 mg of siltuximab.

Do not use SYLVANT® if:

- you have had a severe allergic reaction to SYLVANT®, or any of the other ingredients in SYLVANT®. As with other medicines similar to SYLVANT®, allergic reactions may occur.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SYLVANT®. Talk about any health conditions or problems you may have, including if you:

- have an infection. This is because SYLVANT® may lower your ability to feel or fight infections, and infections may get worse, such as pneumonia or blood poisoning (also called sepsis). Tell your doctor right away if you get any symptoms of infection during treatment with SYLVANT®, including: cough or flu-like symptoms; feeling tired or unwell; painful, red or hot skin; or fever.

- have HIV (AIDS) or HHV-8 infection. Your doctor will do tests to confirm you do not have either of these, before starting treatment with SYLVANT®.
- A history of stomach or bowel disease such as ulcers, diverticulitis or colitis (Crohn's disease). This is because several patients treated with SYLVANT® but who did not have Castleman's disease had serious side effects called perforated bowel (holes in the bowel).
- are due to have a vaccine. This is because SYLVANT® may interfere with some vaccines. Your doctor may give you recommended vaccinations before you start SYLVANT® treatment.
- have high level of fats in your blood (high cholesterol or triglycerides). This is because SYLVANT® may increase these levels or interact with medications used to treat these high levels. Your doctor may prescribe a medicine to help treat this.
- have kidney disease.
- have liver disease or changes that show up in blood tests of the liver.
- are pregnant or could become pregnant. You should not get pregnant while on SYLVANT® or within 3 months after receiving treatment with SYLVANT®. Babies born to mothers treated with SYLVANT® may have more infections, and you should talk to your doctor before live vaccines are given to these infants. Talk to your doctor about stopping SYLVANT® if you are pregnant or planning to become pregnant. You should use effective birth control during treatment and for at least 3 months after stopping SYLVANT® therapy.
- are on birth control pills or other hormone replacement. SYLVANT® can make hormone treatments including birth-control pills less effective, and you could become pregnant even though you don't miss a pill. You should use additional birth control during treatment and for at least 3 months after stopping SYLVANT® therapy.
- men receiving SYLVANT® and their female partners must use effective birth control during and for at least 3 months after treatment with SYLVANT®.
- are breastfeeding or planning to breastfeed. It is not known if SYLVANT® passes into breast milk, but your breastfed baby may also be at increased risk for infections. You and your doctor should decide if you will take SYLVANT® or breast-feed.
- have any allergies to this drug or its ingredients.
- have hypertension (high blood pressure).
- have high level of red blood cells
- get any new health problems or if any of them get worse

Allergic reactions
Tell your doctor immediately if you have a severe allergic reaction during or after the infusion. Signs include: difficulty breathing, chest tightness, wheezing, severe dizziness or lightheadedness, swelling of the lips or skin rash.

Infections
You may be more likely to get infections while you are being treated with SYLVANT®. These infections may be serious, such as pneumonia or blood poisoning (also called "sepsis"). Tell your doctor immediately, if you get any signs of infection during treatment with SYLVANT®. Signs include:
- cough
- flu-like symptoms
- feeling unwell
- red or hot skin

- fever

Your doctor may stop giving you SYLVANT® right away.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Taking SYLVANT® with some medicines may increase or decrease their effects, or cause side effects. The following may interact with SYLVANT®:
- Theophylline (used to treat asthma)
- Warfarin (used to stop your blood from clotting or to thin your blood)
- Statins such as atorvastatin (used for high cholesterol)
- Cyclosporine (used for organ transplants)
- Hormone treatments including birth control pills.

Your doctor will tell you whether you can continue the medicines you are taking or reduce the dose.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before you are given SYLVANT®.

How to take SYLVANT®:
SYLVANT® will be given to you by your doctor or nurse, in a hospital or clinic. SYLVANT® is given as an "intravenous infusion" (a drip into a vein, usually in your arm) slowly over one hour. During the infusion of SYLVANT®, you will be checked for side effects.

Usual dose:
SYLVANT® is dosed by body weight, which is usually 11 mg per kilogram. Your dose may be adjusted by your doctor.

Overdose:
As this medicine will be given to you by your doctor or nurse, it is unlikely that you will be given too much. There are no known side effects of having too much SYLVANT®.

If you think you have been given too much SYLVANT®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you forget or miss your appointment to be given SYLVANT®, make another appointment as soon as possible.

What are possible side effects from using SYLVANT®?
These are not all the possible side effects you may feel when taking SYLVANT®. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of SYLVANT® include: infections, colds, itching, and rash.

Other common side effects include:

- drop in the number of white blood cells (neutropenia) which can decrease your body's ability to fight infections
- drop in the number of platelets (thrombocytopenia) which can cause easy bleeding and bruising
- high fat levels in your blood (cholesterol and triglycerides)
- high level of 'uric acid' in the blood which may cause gout
- abnormal kidney function test
- swelling in the arms, legs, neck or face
- pain in joints, arms or legs
- sore throat
- high blood pressure
- low blood pressure
- common cold
- stomach pain or discomfort
- weight gain
- constipation
- diarrhea
- nausea
- vomiting
- heartburn
- ulcers (sores) in the mouth
- dizziness

In addition there are possible serious side effects and they are listed in the table below.

Serious side effects and what to do about them			
Symptom / effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Common (up to 1 in 10 people)			
As with other medications similar to SYLVANT®, allergic reactions may occur. Tell your doctor immediately if you notice signs of severe allergic (hypersensitivity) reaction such as trouble swallowing, wheezing, feeling dizzy or lightheaded, hives, or swelling of the lips, tongue or mouth. If any of these occur, SYLVANT® may need to be stopped immediately and you may need emergency treatment.		✓	✓
High blood pressure. You may not have any symptoms, or you could have headache, blurred or double vision		✓	✓
Rash		✓	✓
Uncommon (less than 1% of patients)			
Fever, easy bleeding, easy bruising		✓	✓
Stomach pain, blood in stool		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect® (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store SYLVANT® in the refrigerator. Do not use SYLVANT® after the expiration date stated on the label and carton, even if it is stored properly.

Keep out of reach and sight of children.

If you want more information about SYLVANT®:

- Talk to your healthcare professional
- For questions or concerns, please contact the manufacturer, Janssen Inc., at www.janssen.com/canada
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (http://www.janssen.com/canada), or by calling 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by:
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