Siltuximab (All Populations Monograph)

Indications/Dosage

Labeled

- multicentric Castleman disease

Off-Label, Recommended

- coronavirus disease 2019 (COVID-19) †
- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection †

† Off-label indication

INVESTIGATIONAL USE: For adjunctive use in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection†, the virus that causes coronavirus disease 2019 (COVID-19)†

Intravenous dosage

- Adults

Efficacy has not been established. A single dose of 11 mg/kg via intravenous infusion over 1 hour is being evaluated. In 1 study, a second dose could be administered at the physician's discretion; a total of 5 patients received a second dose [dosing interval: 2 days (n = 3/5), 3 days (n = 2/5)]. [65194] [65223] [65224] [65227]

For the treatment multicentric Castleman disease (MCD) in patients who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative

NOTE: The FDA has designated siltuximab as an orphan drug for Castleman disease.
Intravenous dosage

- Adults

11 mg/kg IV over 1 hour every 3 weeks until treatment failure. Prior to starting siltuximab therapy, verify that the absolute neutrophil count is $1 \times 10^9$ cells/L or greater, the platelet count is $75 \times 10^9$ cells/L or greater, and the hemoglobin concentration is less than 17 grams/dL. Interrupt the siltuximab infusion for mild or moderate infusion-related reactions. The response (complete response (CR) plus partial response (PR)) rate with improvement or stabilization of disease-related symptoms for at least 18 weeks (primary endpoint) was significantly higher in patients who received siltuximab ($n = 53$; median duration of therapy, 19 cycles) compared with placebo ($n = 26$) (34% vs. 0%; $p = 0.0012$) for the treatment of multicentric Castleman disease in a multinational, randomized, double-blind trial; the median duration of response was 383 days (range, 232 to 676 days). In this study, 55% of patients in the siltuximab arm had received prior systemic therapy. During the study, all patients received best supportive care specified by institutional guidelines. The response rates (evaluated by independent review using modified Cheson criteria) were 39% (CR, $n = 2$; PR, $n = 18$) and 4% (PR, $n = 1$) in the siltuximab and placebo arms, respectively ($p = 0.0022$); the time to response was 155 days (range, 44 to 742 days) in patients who received siltuximab. The durable symptomatic response rates (based on a disease-related overall symptom score evaluated by investigators) were 57% ($n = 30$) and 19% ($n = 5$) in the siltuximab and placebo arms, respectively ($p = 0.0018$); the time to response was 170 days (range, 67 to 274 days) in patients who received siltuximab. Of note, no patients with the hyaline vascular disease subtype achieved a durable tumor and symptomatic response evaluated by independent review. At a median follow-up of 422 days (range, 55 to 1,051 days), the median time to treatment failure was not reached in the siltuximab arm and was 134 days in the placebo arm ($p = 0.0084$). The 1-year overall survival rate was 100% and 92% in the siltuximab and placebo arms, respectively.[59439]

Therapeutic Drug Monitoring

Management of Treatment-Related Toxicity

Hematologic Toxicity

Verify that the absolute neutrophil count (ANC) is $1 \times 10^9$ cells/L or greater, the platelet count is $50 \times 10^9$ cells/L or greater, and the hemoglobin concentration is less than 17 g/dL prior to giving the next siltuximab dose. Delay therapy until the hematologic criteria are met; do not reduce the siltuximab dose.[57062]

Maximum Dosage Limits

- Adults

11 mg/kg IV.
• Geriatric
  11 mg/kg IV.
• Adolescents
  Safety and efficacy have not been established.
• Children
  Safety and efficacy have not been established.
• Infants
  Safety and efficacy have not been established.
• Neonates
  Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

No dosage adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Siltuximab use has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C).[57062]

Patients with Renal Impairment Dosing

No dosage adjustment is necessary in patients with renal impairment (creatinine clearance of 15 to 90 mL/min). Siltuximab use has not been evaluated sufficiently in patients with end-stage renal disease.[57062]

† Off-label indication

Revision Date: 04/09/2020 12:17:25 PM

References


**Description/Classification**

**Description**

Siltuximab is an interleukin-6 antagonist indicated for the treatment of adult patients with multicentric Castleman disease who are human immunodeficiency virus-negative and human herpesvirus-8-negative. Monitor patients for signs and symptoms of infection; do not start siltuximab in patients with a severe active infection. Severe infusion-related reactions may occur; therefore, administer siltuximab in a setting that provides resuscitation equipment, medication, and personnel trained to provide resuscitation.[57062]

**Updates for coronavirus disease 2019 (COVID-19):**

Based on preliminary data from a study of another IL-6 receptor antibody, studies have begun to evaluate the use of siltuximab for COVID-19.[65194][65223][65224][65227]
Classifications

- Antineoplastic and Immunomodulating Agents
  - Antineoplastics
    - Antineoplastic Monoclonal Antibodies
    - Immunomodulatory Monoclonal Antibodies
    - Monoclonal Antibodies that Target Interleukin 6 (IL-6)

Revision Date: 04/09/2020 12:06:37 PM

References


Administration Information

General Administration Information

For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Injectable Administration

Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.
Intravenous Administration

Reconstitution:

- Allow the lyophilized vial(s) to come to room temperature over approximately 30 minutes; vials should remain at room temperature for the duration of the preparation.
- A 21-gauge, 1 and 1/2 inch needle is recommended for preparation.
- Add 5.2 mL of Sterile Water for Injection to the 100-mg vial and 20 mL of Sterile Water for Injection to the 400-mg vial for a final vial concentration of 20 mg/mL.
- Gently swirl the reconstituted vial; do NOT shake or swirl vigorously.
- Allow the lyophilized powder to completely dissolve; powder should dissolve in less than 60 minutes.
- Storage following reconstitution: further dilute the vial contents within 2 hours of reconstitution.

Dilution:

- Withdraw the appropriate volume (mL) from the siltuximab 20 mg/mL vials for the calculated dose; discard any unused portion left in the vial.
- Dilute the calculated dose in 5% Dextrose Injection to a total infusion bag volume of 250 mL; this may be achieved by withdrawing a volume equal to the calculated volume of siltuximab from a 250-mL bag of 5% Dextrose Injection.
- Gently invert the bag to mix the solution after slowly adding the calculated volume to the 5% Dextrose Injection solution.
- Infusion bags must be made of polyvinyl chloride (PVC), polyolefin, polypropylene, or polyethylene (PE); PE bottles may also be used.
- Storage after dilution: use within 4 hours after dilution.

Intravenous Infusion:

- Administer over 1 hour using an administration set lined with PVC, polyurethane, or PE containing a 0.2 micron inline polyethersulfone (PES) filter.
- Do not infuse concomitantly in the same IV line with other agents.
- Do not store any unused portion of the infusion solution.[57062]

Clinical Pharmaceutics Information

From Trissel's 2™ Clinical Pharmaceutics Database

Siltuximab

1. pH Range

   pH is approximately 5.2 (reconstituted).
Adverse Reactions

- abdominal pain
- anaphylactoid reactions
- antibody formation
- back pain
- chest pain (unspecified)
- constipation
- cytokine release syndrome
- diarrhea
- dizziness
- edema
- edema
- erythema
- flushing
- gastroesophageal reflux
- GI perforation
- headache
- hypercholesterolemia
- hypertension
- hypertriglyceridemia
- hyperuricemia
- hyperuricemia
- hypotension
- hypotension
- infection
- infection
- infusion-related reactions
- infusion-related reactions
- maculopapular rash
- maculopapular rash
- nausea
- nephrotoxicity
- neutropenia
- oral ulceration
- palpitations
- pharyngitis
- pruritus
- psoriasis
- rash
- rash
- skin hyperpigmentation
- thrombocytopenia
- thrombocytopenia
- vomiting
- weight gain
- weight gain
- xerosis

Dermatologic adverse events that were reported more often in patients with multicentric Castleman disease who received siltuximab plus best supportive care (BSC) (n = 53) compared with placebo plus BSC (n = 26) in a randomized, phase 2 study included rash (28% vs. 12%; grade 3 or 4, 2% vs. 0%), pruritus (28% vs. 8%), skin hyperpigmentation (4% vs. 0%), eczema (4% vs. 0%), psoriasis (4% vs. 0%), and xerosis (4% vs. 0%). Rash included generalized rash, maculopapular rash, and pruritic rash.[57062]
Infection has been reported with siltuximab therapy. Monitor patients closely for signs or symptoms of infection during therapy. If an infection develops, start anti-infective therapy and hold siltuximab until the infection resolves. Lower respiratory tract infection (8% vs. 4%; grade 3 or 4, 4% vs. 4%) and upper respiratory tract infection (26% vs. 15%; grade 3 or 4, 2% vs. 4%) were reported more often in patients with multicentric Castleman disease (MCD) who received siltuximab plus best supportive care (BSC) (n = 53) compared with placebo plus BSC (n = 26) in a randomized, phase 2 study. Additionally, naso-pharyngitis and urinary tract infection have been reported commonly in patients with MCD who received siltuximab in clinical studies.[57062]

Hematologic adverse events have been reported in patients who received siltuximab in clinical trials. Monitor complete blood counts prior to each dose for the first 12 months of therapy and then every 3 dosing cycles thereafter. After the first dose of therapy, ensure that the ANC is 1 x 10^9 cells/L or greater, the platelet count is 50 x 10^9 cells/L or greater, and the hemoglobin concentration is less than 17 grams/dL prior to giving each siltuximab dose. Thrombocytopenia was reported in 9% of patients who received siltuximab plus best supportive care (BSC) (n = 53) compared with 4% of patients with multicentric Castleman disease (MCD) who received placebo plus BSC (n = 26) in a randomized, phase 2 study; grade 3 or 4 thrombocytopenia occurred in 4% of siltuximab-treated patients. Additionally, neutropenia has been reported commonly in patients with MCD who received siltuximab in clinical studies.[57062]

Edema was reported in 26% of patients with multicentric Castleman disease who received siltuximab plus best supportive care (BSC) (n = 53) and 27% of patients who received placebo plus BSC (n = 26) in a randomized, phase 2 study; grade 3 or 4 edema occurred in 8% and 0% of patients, respectively.[57062]

Gastrointestinal (GI) adverse events such as abdominal pain, diarrhea, gastroesophageal reflux disease, nausea, mouth/oral ulceration, and vomiting have been reported commonly in patients with multicentric Castleman disease (MCD) who received siltuximab in clinical studies. Additionally, GI perforation has been reported with siltuximab use. Promptly evaluate patients who have symptoms suggestive of GI perforation. Constipation (8% vs. 4%) and oropharyngeal pain (8% vs. 4%) were reported more often in patients with MCD who received siltuximab plus best supportive care (BSC) (n = 53) compared with placebo plus BSC (n = 26) in a randomized, phase 2 study.[57062]

Metabolic adverse events that were reported more often in patients with multicentric Castleman disease who received siltuximab plus best supportive care (BSC) (n = 53) compared with placebo plus BSC (n = 26) in a randomized, phase 2 study included hypertriglyceridemia (8% vs. 0%), hypercholesterolemia (4% vs. 0%), hyperuricemia (11% vs. 0%; grade 3 or 4, 2% vs. 0%) and weight gain (19% vs. 0%; grade 3 or 4, 2% vs. 0%).[57062]

Headache was reported in 8% of patients with multicentric Castleman disease (MCD) who received siltuximab plus best supportive care (BSC) (n = 53) compared with 4% of patients who received placebo plus BSC (n = 26) in a randomized, phase 2 study. Additionally, dizziness has been reported commonly in patients with MCD who received siltuximab in clinical studies.[57062]

Hypotension was reported in 4% of patients with multicentric Castleman disease (MCD) who received siltuximab plus best supportive care (BSC) (n = 53) compared with 0% of patients who received placebo plus BSC (n = 26) in a randomized, phase 2 study; grade 3 or 4 hypotension occurred in 2% of siltuximab-treated patients. Additionally, hypertension has been reported commonly in patients with MCD who received siltuximab in clinical studies.[57062]

Hypersensitivity reactions including anaphylactoid reactions have been reported with siltuximab therapy. One of 945 patients who received siltuximab in clinical studies experienced an
anaphylactic reaction. If anaphylaxis, severe allergic reactions, or cytokine release syndrome occurs during therapy, immediately stop the siltuximab infusion and do not resume therapy.[57062]

Infusion-related reactions were reported in 5.1% of patients who received single-agent siltuximab in clinical studies (n = 254); 0.8% of patients experienced grade 3 or 4 infusion-related reactions. Symptoms may include back pain, chest pain (unspecified) or discomfort, nausea, vomiting, flushing, erythema, and palpitations. Interrupt the siltuximab infusion for mild or moderate infusion-related reactions; therapy may be resumed at a lower infusion rate if the reaction resolves. The use of antihistamines, acetaminophen, and corticosteroids may be considered to help prevent or lessen infusion-related reactions. If the patient does not tolerate the siltuximab infusion despite the use of prophylactic medications, discontinue therapy. Infusion-related or hypersensitivity reactions were reported in 6.3% of patients treated with siltuximab in a long-term safety trial (n = 19); grade 3 or 4 reactions occurred in 1.3% of these patients.[57062]

Antibody formation has been reported in 0.9% of patients who received siltuximab in clinical trials (n = 432). None of 243 patients who were evaluated using the antigen-bridging enzyme immunoassay method experienced an anti-therapeutic antibody (ATA) response. However, 4 of 189 patients evaluated using the electrochemiluminescence-based immunoassay method tested positive for ATA; none of these patients had neutralizing antibodies.[57062]

Nephrotoxicity, specifically renal impairment, was reported in 8% of patients with multicentric Castleman disease who received siltuximab plus best supportive care (BSC) (n = 53) compared with 0% of patients who received placebo plus BSC (n = 26) in a randomized, phase 2 study. [57062]

References


Contraindications/Precautions

Absolute contraindications are italicized.

- breast-feeding
- contraception requirements
- diverticulitis
- GI perforation
- infants
- infection
- infusion-related reactions
- neonates
- neutropenia
- peptic ulcer disease
- pregnancy
- reproductive risk
- thrombocytopenia
- vaccination

Siltuximab use is contraindicated in patients who have had a severe hypersensitivity reaction to siltuximab or any components of the product. If anaphylaxis, severe allergic reactions, or cytokine release syndrome occur during therapy, immediately stop the siltuximab infusion and do not resume therapy. Only give siltuximab therapy in a setting that provides resuscitation equipment,
medication, and personnel trained to provide resuscitation. Infusion-related reactions have been reported. Symptoms include back pain, chest pain/discomfort, nausea, vomiting, flushing, erythema, and palpitations. Interrupt the siltuximab infusion for mild or moderate infusion-related reactions; therapy may be resumed at a slower infusion rate if the reaction resolves. The use of antihistamines, acetaminophen, and corticosteroids may be considered to help prevent or lessen infusion-related reactions. If the patient does not tolerate the siltuximab infusion despite the use of prophylactic medications, discontinue therapy.[57062]

Siltuximab may mask signs and symptoms of infection (e.g., suppress fever and/or C-reactive protein (CRP) levels) or lower resistance to infection due to its immunosuppressive effects. Do not administer siltuximab to patients with severe infections until the infection resolves. Monitor patients closely for signs or symptoms of infection during therapy. If an infection develops during therapy, start anti-infective therapy and hold siltuximab until the infection resolves.[57062]

GI perforation has been reported with siltuximab therapy. Use siltuximab with caution in patients who may be at increased risk for GI perforation such as patients with diverticulitis or peptic ulcer disease. Promptly evaluate patients who have symptoms suggestive of GI perforation.[57062]

Hematologic adverse events (e.g., neutropenia and thrombocytopenia) have been reported with siltuximab therapy. Monitor complete blood counts prior to each dose for the first 12 months of therapy and then every 3 dosing cycles thereafter. Prior to starting siltuximab, ensure that the absolute neutrophil count (ANC) is 1 x 10^9 cells/L or greater, the platelet count is 75 x 10^9 cells/L or greater, and the hemoglobin concentration is less than 17 grams/dL. Ensure that the ANC is 1 x 10^9 cells/L or greater, the platelet count is 50 x 10^9 cells/L or greater, and the hemoglobin concentration is less than 17 grams/dL prior to giving subsequent siltuximab doses.[57062]

Avoid vaccination with live vaccines in patients receiving siltuximab as IL-6 inhibition may interfere with the normal immune response to new antigens. Infants and neonates born to pregnant women who were treated with siltuximab may have an increased risk of infection; administer live vaccines to these patients with caution.[57062]

Based on findings in animal reproduction studies, siltuximab may cause fetal harm when administered during human pregnancy. There are no available data on siltuximab use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Females of reproductive potential should avoid pregnancy during siltuximab therapy. Advise pregnant women of the potential fetal risk. Monoclonal antibodies appear to cross via the placenta. In cynomolgus monkey reproduction studies, siltuximab administration during organogenesis resulted in fetal serum concentrations that were similar to maternal concentrations at exposures above those occurring at the maximum recommended human dose of 11 mg/kg given every 3 weeks.[57062]

Counsel patients about the reproductive risk and contraception requirements during siltuximab treatment. Females of reproductive potential should avoid pregnancy and use effective contraception during and for 3 months after treatment with siltuximab.[57062]

Because of the potential for serious adverse reactions in the breast-fed child, including gastrointestinal perforation, breast-feeding is not recommended during siltuximab treatment and for 3 months after the last dose. There are no data on the presence of siltuximab in human milk, the effects on the breast-fed child, or the effects on milk production.[57062]
Mechanism of Action

Siltuximab is a human-mouse chimeric monoclonal antibody that binds human interleukin-6 (IL-6) and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors. IL-6 is a proinflammatory cytokine and overproduction of IL-6 has been linked to systemic manifestations in patients with multicentric Castleman disease (MCD).[57062]

Pharmacokinetics

Siltuximab is administered intravenously (IV). The pharmacokinetic profile is a linear two-compartment intravenous model with first-order elimination. Based on population pharmacokinetic analyses, the volume of distribution in a male patient weighing 70 kg was 4.5 L (coefficient of variance (CV), 20%), the clearance was 0.23 L/day (CV, 51%), and the terminal half-life after the first IV infusion was 20.6 days (range, 14.2 to 29.7 days).

Affected cytochrome P450 isoenzymes: CYP3A4

Siltuximab has not been evaluated in in vitro or in vivo drug interaction studies. However, inhibition of IL-6 signaling may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates. If siltuximab is administered with a CYP450 substrate with a narrow therapeutic index (e.g., warfarin, cyclosporine, theophylline), therapeutic drug monitoring is recommended and a dose adjustment of the CYP450 substrate may be necessary. Use siltuximab with caution in patients who are receiving a CYP3A4 substrate in which a decrease in effectiveness would be undesirable (e.g., oral contraceptives, lovastatin, atorvastatin).[57062]

Route-Specific Pharmacokinetics

- Intravenous Route
In patients with multicentric Castleman disease, the steady-state mean Cmax value was 332 micrograms (mcg)/mL (coefficient of variance (CV), 42%) and the mean Cmin value was 84 mcg/mL (CV, 78%) following siltuximab 11 mg/kg IV over 1 hour once every 3 weeks. Steady state levels are achieved by the sixth infusion following siltuximab IV once every 3 week dosing; it accumulates about 1.7-fold compared to a single dose. Siltuximab demonstrates approximately dose proportional pharmacokinetics over the dose range of 2.8 to 11 mg/kg.[57062]

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**Special Populations**

- **Hepatic Impairment**

  Mild or moderate hepatic impairment did not significantly affect the apparent clearance of siltuximab in a population pharmacokinetic (PK) analysis (n = 377); the influence of severe hepatic impairment on the PK parameters of siltuximab has not been evaluated. In this analysis, 72 patients with mild pre-existing hepatic impairment (Child-Pugh class A) and 3 patients with moderate pre-existing hepatic impairment (Child-Pugh class B) were compared with 302 patients who had normal hepatic function.[57062]

- **Renal Impairment**

  Renal impairment did not significantly affect the apparent clearance of siltuximab in a population pharmacokinetic (PK) analysis (n = 377); the influence of end-stage renal disease (ESRD) on the PK parameters of siltuximab cannot be determined because only 1 patient had ESRD. In this analysis, 122 patients with mild pre-existing renal impairment (creatinine clearance (CrCl), 60 to 89 mL/min), 75 patients with moderate pre-existing renal impairment (CrCl, 30 to 59 mL/min), and 3 patients with severe pre-existing renal impairment (CrCl, 15 to 29 mL/min) were compared with 176 patients who had normal renal function (CrCl, 90 mL/min or greater).[57062]

- **Geriatric**

  Age (range, 18 to 85 years) did not affect siltuximab exposure in a population pharmacokinetic analysis (n = 378).[57062]

- **Gender Differences**

  Gender did not affect siltuximab exposure in a population pharmacokinetic analysis (females, n = 175; males, n = 203).[57062]

- **Obesity**

  Weight correlated with siltuximab clearance in a population pharmacokinetic analysis (n = 378); therefore, weight-based dosing is appropriate.[57062]
Pregnancy/Breast-feeding

Pregnancy

Based on findings in animal reproduction studies, siltuximab may cause fetal harm when administered during human pregnancy. There are no available data on siltuximab use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Females of reproductive potential should avoid pregnancy during siltuximab therapy. Advise pregnant women of the potential fetal risk. Monoclonal antibodies appear to cross via the placenta. In cynomolgus monkey reproduction studies, siltuximab administration during organogenesis resulted in fetal serum concentrations that were similar to maternal concentrations at exposures above those occurring at the maximum recommended human dose of 11 mg/kg given every 3 weeks.[57062]

Breast-Feeding

Because of the potential for serious adverse reactions in the breast-fed child, including gastrointestinal perforation, breast-feeding is not recommended during siltuximab treatment and for 3 months after the last dose. There are no data on the presence of siltuximab in human milk, the effects on the breast-fed child, or the effects on milk production.[57062]

References


Interactions

Level 1 (Severe)

• Live Vaccines

Level 2 (Major)

• Clozapine

Level 3 (Moderate)
Level 4 (Minor)

- Amlodipine; Atorvastatin
- Atorvastatin
- Atorvastatin; Ezetimibe
- Lovastatin
- Lovastatin; Niacin

Amlodipine; Atorvastatin: (Minor) Caution is warranted in patients with co-administered CYP3A4 substrates, such as atorvastatin, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Apixaban: (Moderate) Monitor for a decrease in efficacy of apixaban if used with siltuximab. Until more data are available, consider using an anticoagulant without dependence on CYP450 enzymes for metabolism (e.g., heparins, edoxaban). The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines such as IL-6 during chronic inflammation. It is expected that the activity of CYP450 enzymes could increase to normal concentrations during treatment with an IL-6 antagonist such as siltuximab; these effects on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. In vitro, siltuximab has the potential to affect expression of multiple CYP enzymes [including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4]. Apixaban is a substrate for CYP3A4. [52739] [57062] [65210]

Atorvastatin: (Minor) Caution is warranted in patients with co-administered CYP3A4 substrates, such as atorvastatin, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to
metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Atorvastatin; Ezetimibe: (Minor) Caution is warranted in patients with co-administered CYP3A4 substrates, such as atorvastatin, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Clozapine: (Major) It is unclear if concurrent use of other drugs known to cause neutropenia (e.g., antineoplastic agents) increases the risk or severity of clozapine-induced neutropenia. Because there is no strong rationale for avoiding clozapine in patients treated with these drugs, consider increased absolute neutrophil count (ANC) monitoring and consult the treating oncologist. [28262]

Cyclosporine: (Moderate) Use siltuximab and cyclosporine together with caution; monitor cyclosporine levels and adjust the dose of cyclosporine as necessary. Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as cyclosporine, may have fluctuations in drug levels and therapeutic effect when siltuximab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. [57062]

Dienogest; Estradiol valerate: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as cyclosporine, may have fluctuations in drug levels and therapeutic effect when siltuximab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. [57062]

Drospirenone: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as cyclosporine, may have fluctuations in drug levels and therapeutic effect when siltuximab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. [57062]

Drospirenone; Estradiol: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as cyclosporine, may have fluctuations in drug levels and therapeutic effect when siltuximab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. [57062]

Drospirenone; Ethinyl Estradiol: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are
CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Drospirenone; Ethinyl Estradiol; Levomefolate: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Estradiol; Levonorgestrel: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Estradiol; Norethindrone: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Estradiol; Norgestimate: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Ethinyl Estradiol: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Ethinyl Estradiol; Desogestrel: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Ethinyl Estradiol; Ethynodiol Diacetate: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would
be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Etonogestrel:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Levonorgestrel:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norelgestromin:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norethindrone Acetate:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would
be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norethindrone:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norethindrone; Ferrous fumarate:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norgestimate:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Ethinyl Estradiol; Norgestrel:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Leuprolide; Norethindrone:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli,
including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Levonorgestrel:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Live Vaccines:** (Severe) Do not administer live vaccines to siltuximab recipients; no data are available regarding the risk of secondary transmission of infection by live vaccines in patients receiving siltuximab. Before initiation of siltuximab therapy, consider completion of all age appropriate vaccinations per current immunization guidelines. Siltuximab recipients may receive inactivated vaccines, but the immune response to vaccines or toxoids may be decreased. [43236] [57062]

**Lovastatin:** (Minor) Caution is warranted in patients with co-administered CYP3A4 substrates, such as lovastatin, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Lovastatin; Niacin:** (Minor) Caution is warranted in patients with co-administered CYP3A4 substrates, such as lovastatin, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Mestranol; Norethindrone:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Norethindrone:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

**Norgestrel:** (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]
in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Oral Contraceptives: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Rivaroxaban: (Moderate) Monitor for a decrease in efficacy of rivaroxaban if used with siltuximab. Until more data are available, consider using an anticoagulant without dependence on CYP450 enzymes for metabolism (e.g., heparins, edoxaban). The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines such as IL-6 during chronic inflammation. It is expected that the activity of CYP450 enzymes could increase to normal concentrations during treatment with an IL-6 antagonist such as siltuximab; these effects on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. In vitro, siltuximab has the potential to affect expression of multiple CYP enzymes [including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4]. Rivaroxaban is a substrate for CYP3A4/5. [44854] [57062] [65210]

Segesterone Acetate; Ethinyl Estradiol: (Moderate) Caution is warranted in patients with co-administered CYP3A4 substrates, such as oral contraceptives, in which a decreased effect would be undesirable. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Theophylline, Aminophylline: (Moderate) Use siltuximab and theophylline together with caution; monitor theophylline levels and adjust the dose of theophylline as necessary. Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as theophylline, may have fluctuations in drug levels and therapeutic effect when siltuximab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. [57062] (Moderate) When siltuximab is initiated or discontinued in patients being treated with CYP450 substrates with a narrow therapeutic index, such as theophylline, aminophylline, monitor appropriately for effect and drug concentrations as necessary. Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli, including cytokines such as interleukin-6 (IL-6). Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. The effect of siltuximab on CYP450 enzyme activity can persist for several weeks after stopping therapy. [57062]

Warfarin: (Moderate) Monitor the INR if siltuximab is coadministered with warfarin due to the potential for decreased warfarin efficacy; adjust the dose of warfarin as necessary. Inhibition of IL-6 signaling by siltuximab may restore CYP450 activities to higher levels leading to increased
metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as warfarin, may have fluctuations in drug levels and therapeutic effect when siltuximab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping siltuximab. [28549] [57062]

Revision Date: 04/14/2020 02:26:00 AM

References

28262 – Clozaril (clozapine) tablets package insert. Rosemont, PA: HLS Therapeutics (USA), Inc. (Clozaril is a registered trademark of Novartis AG); 2017 Feb.


Monitoring Parameters

- CBC with differential

IV Compatibility of Siltuximab with:

Legend

.green = Compatible
.red = Incompatible
.yellow = Results uncertain, variable or dependent on conditions
.ND = No Data Available

From Trissel's 2™ Clinical Pharmaceutics Database
### US Drug Names

- Sylvant

### Global Drug names

**Australia**
- Sylvant - (Janssen-Cilag)

**Belgium**
- Sylvant - (Janssen-Cilag)

**Brazil**
- Sylvant - (Janssen-Cilag)

**Canada**
- Sylvant - (Janssen)

**Czech Republic**
- Sylvant - (Janssen-Cilag)

**Denmark**
- Sylvant - (Janssen)

**Finland**
- Sylvant - (Janssen-Cilag)

**France**
- Sylvant - (Janssen-Cilag)

**Germany**
- Sylvant - (Janssen-Cilag)

**Greece**
- Sylvant - (Janssen-Cilag)

**Hong Kong**
• Sylvant - (Johnson & Johnson)

Hungary
• Sylvant - (Janssen-Cilag)

Ireland
• Sylvant - (Janssen-Cilag)

Israel
• Sylvant - (Janssen-Cilag)

Netherlands
• Sylvant - (Janssen-Cilag)

New Zealand
• Sylvant - (Janssen-Cilag)

Norway
• Sylvant - (Janssen-Cilag)

Poland
• Sylvant - (Janssen-Cilag)

Singapore
• Sylvant - (Janssen-Cilag)

Spain
• Sylvant - (Janssen-Cilag)

Sweden
• Sylvant - (Janssen-Cilag)

Switzerland
• Sylvant - (Janssen-Cilag)

United Kingdom
• Sylvant - (Janssen-Cilag)