SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

SYLVANT 100 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Siltuximab is a chimeric (human-murine) immunoglobulin G1κ (IgG1κ) monoclonal antibody produced in a Chinese hamster ovary (CHO) cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

The product is a freeze-dried white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

This medicinal product should be administered by qualified healthcare professionals and under appropriate medical supervision.

Posology

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

Treatment criteria

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

Table 1: 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
Haemoglobin[a]	< 170 g/L (10.6 mmol/L)	< 170 g/L (10.6 mmol/L)

[a] SYLVANT may increase haemoglobin levels in MCD patients

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

If the patient develops a severe infusion related reaction, anaphylaxis, severe allergic reaction, or cytokine release syndrome related to the infusion, further administration of SYLVANT should be discontinued. Discontinuing the medicinal product should be considered if there are more than 2 dose delays due to toxicities related to the treatment during the first 48 weeks.

Special populations

Elderly patients

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

Renal and/or hepatic impairment

No formal studies have been conducted to investigate the PK of siltuximab in patients with renal or hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of siltuximab in children aged 17 years and younger have not been established.

No data are available.

Method of administration

Siltuximab must be administered as an intravenous infusion.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Concurrent active serious infections

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

Hypoglobulinaemia was observed in 4 to 11.3% of patients in the clinical study.

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

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

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

Vaccinations

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

Lipid parameters

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

Infusion related reactions and hypersensitivity

During intravenous infusion of SYLVANT, mild to moderate infusion reactions may improve following slowing of or stopping the infusion. Upon resolution of the reaction, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, acetaminophen, and corticosteroids may be considered. For patients who do not tolerate the infusion following these interventions, SYLVANT should be discontinued. During or following infusion, treatment should be discontinued in patients who have severe infusion related hypersensitivity reactions (e.g., anaphylaxis). The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medicinal product should be available to treat anaphylaxis if it occurs (see section 4.8).

Malignancy

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

Gastrointestinal perforation

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

Hepatic impairment

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

Paediatric population

No interaction studies have been performed in this population.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no data from the use of siltuximab in pregnant women. Studies in animals with siltuximab have shown no adverse effect on pregnancy or on embryofetal development (see section 5.3). Siltuximab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Siltuximab should be given to a pregnant woman only if the benefit clearly outweighs the risk.

As with other immunoglobulin G antibodies, siltuximab crosses the placenta as observed in studies in monkeys. Consequently, infants born to women treated with siltuximab may be at increased risk of infection, and caution is advised in the administration of live vaccines to these infants (see section 4.4).

Breast-feeding

It is unknown whether siltuximab is excreted in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or discontinue/abstain from siltuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Effects of siltuximab on fertility have not been evaluated in humans. Available non-clinical data do not suggest an effect on fertility under siltuximab treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Infections (including upper respiratory tract infections), pruritus, rash, arthralgia, and diarrhoea were the most common adverse reactions , occurring in > 20% of siltuximab-treated patients in Castleman’s disease (CD) clinical studies. The most serious adverse reaction associated with the use of siltuximab was anaphylactic reaction.

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

Table 2 reflects the frequencies of identified adverse reactions in the 87 MCD patients (Study 1, Study 2 and Study 3) treated at the recommended dosage of 11 mg/kg every 3 weeks (details provided in section 5.1).

Tabulated list of adverse reactions

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

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

System organ class Frequency	**Adverse reaction**
Infections and infestations	
very common	Upper respiratory tract infection, urinary tract infection, nasopharyngitis
Blood and lymphatic system disorders	
very common	Neutropenia, thrombocytopenia
Immune system disorders	
common	Anaphylactic reaction
Metabolism and nutrition disorders	
very common	Hypertriglyceridaemia, hyperuricaemia
common	Hypercholesterolaemia
Nervous system disorders	
very common	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	
very common	Oropharyngeal pain
Vascular disorders	
very common	Hypertension
Gastointestinal disorders	
very common	Nausea, abdominal pain, vomiting, constipation, diarrhoea, gastroesophageal reflux disease, mouth ulceration
Skin and subcutaneous tissue disorders	
very common	Rash, pruritus, eczema
Musculoskeletal and connective tissue disorders	
very common	Arthralgia, pain in extremity
Renal and urinary disorders	
very common	Renal impairment
General disorders and administration site conditions	
very common	Localised oedema
Investigations	
very common	Weight increased

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

Infusion related reactions and hypersensitivity

In clinical studies, siltuximab was associated with an infusion related reaction or hypersensitivity reaction in 5.1% (severe reaction in 0.8%) of patients treated with siltuximab monotherapy.

In long-term treatment of MCD patients with siltuximab at the recommended dosage of 11 mg/kg every 3 weeks, infusion related reactions or hypersensitivity reactions occurred at a frequency of 6.3% (1.3% for severe reactions).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Siltuximab is a human-mouse chimeric monoclonal antibody that forms high affinity, stable complexes with soluble bioactive forms of human IL-6. Siltuximab prevents the binding of human IL-6 to both soluble and membrane-bound IL-6 receptors (IL-6R), thus inhibiting the formation of the hexameric signaling complex with gp130 on the cell surface. Interleukin-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T-cells and B-cells, lymphocytes, monocytes and fibroblasts, as well as malignant cells. IL-6 has been shown to be involved in diverse

normal physiologic processes such as induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. Overproduction of IL-6, in chronic inflammatory diseases and malignancies has been linked to anaemia and cachexia and has been hypothesised to play a central role in driving plasma cell proliferation and systemic manifestations in patients with CD.

Pharmacodynamic effects

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

Biomarkers

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

Clinical efficacy and safety

Study 1

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

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

In Study 1 a statistically significant difference in independently reviewed durable tumour and symptomatic response rate in the siltuximab arm compared with the placebo arm (34% vs. 0%, respectively; 95% CI: 11.1, 54.8; p = 0.0012) was observed. The overall tumour response rate was evaluated based on modified Cheson criteria both by independent review and investigator assessment.

Key efficacy results from Study 1 are summarised in Table 3.

Table 3: Efficacy endpoints from study 1

Efficacy endpoints	**Siltuximab+BSC***	**Placebo+BSC**	**P-value[a]**
Primary efficacy endpoint			
Durable tumour & symptomatic response (independent review)	18/53 (34.0%)	0/26 (0%)	0.0012
Secondary efficacy endpoints			
Durable tumour & symptomatic response (investigator review)	24/53 (45.3%)	0/26 (0%)	< 0.0001
Best tumour response (independent review)	20/53 (37.7%)	1/26 (3.8%)	0.0022
Best tumour response (investigator assessment)	27/53 (50.9%)	0/26 (0%)	< 0.0001
Time to treatment failure	Not reached	134 days	0.0084; HR 0.418
Haemoglobin increase > 15 g/L (0.9 mmol/L) at Week 13/haemoglobin response-evaluable population	19/31 (61.3%)	0/11 (0%)	0.0002
Duration of tumour & symptomatic response (days) - independent review; median (min, max)	340 (55, 676)[b]	N/A[c]	N/A
Durable complete symptomatic response[d]	13/53 (24.5%)	0/26 (0%)	0.0037
Duration of durable complete symptomatic response (days) median (min, max)	472 (169, 762)[e]	N/A	N/A

* Best Supportive Care

[a] Adjusted for corticosteroid use at randomisation

[b] At the time of primary analysis data for 19 of 20 tumour and symptomatic responders were censored due to on-going response

[c] N/A = "Not applicable", there were no responders in the placebo arm, therefore, duration is not applicable

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

[e] Data from 11 of 13 complete symptomatic responders were censored due to on-going response

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

Haemoglobin response was defined as a change from baseline of ≥ 15 g/L (0.9 mmol/L) at Week 13. A statistically significant difference (61.3% vs. 0% respectively; p = 0.0002) in the haemoglobin response in the siltuximab arm compared with the placebo arm was observed.

Subgroup analyses

Analyses for both primary and secondary endpoints on various subgroups including age (< 65 years and ≥ 65 years); race (White and Non-White); region (North America, Europe, Middle East and Africa, and Asia Pacific); baseline corticosteroid use (yes and no); prior therapy (yes and no); and MCD histology (plasmatic and mixed histology) consistently showed that the treatment effect favoured the siltuximab arm except for the hyaline vascular subgroup in which no patient achieved the definition of the primary endpoint. A consistent treatment effect favouring siltuximab treated patients across all major secondary endpoints was shown in the hyaline vascular subgroup. Select efficacy results from Study 1 in the hyaline vascular subgroup are summarised in Table 4.

Table 4: Select efficacy endpoints for hyaline vascular subgroup from study 1

Efficacy endpoints	**Siltuximab+BSC***	**Placebo+BSC**	**95% CI[a]**
Primary efficacy endpoint			
Durable tumour & symptomatic response (independent review)	0/18 (0%)	0/8 (0%)	(N/A; N/A)[b]
Secondary efficacy endpoints			
Durable tumour & symptomatic response (investigator review)	3/18 (16.7%)	0/8 (0%)	(-25.7; 55.9)
Best tumour response (independent review)	1/18 (5.6%)	1/8 (12.5%)	(-46.7; 35.3)
Best tumour response (investigator assessment)	4/18 (22.2%)	0/8 (0%)	(-20.3; 60.6)
Time to treatment failure	206 days	70 days	(0.17; 1.13)[c]
Haemoglobin increase > 15 g/L (0.9 mmol/L) at Week 13/haemoglobin response-evaluable population	3/7 (42.9%)	0/4 (0%)	(-22.7; 83.7)
Durable complete symptomatic response[d]	3/18 (16.7%)	0/8 (0%)	(-25.7; 55.9)

* Best Supportive Care

[a] 95% confidence interval for the for the difference in proportions

[b] N/A = "Not applicable", there were no responders therefore 95% CI is not applicable

[c] 95% confidence interval for the hazard ratio

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

Study 2

In addition to Study 1, efficacy data are available in patients with CD from a single arm Phase 1 study (Study 2). In this study 37 patients with CD (35 MCD patients) were treated with siltuximab. In the 16 patients with MCD treated with 11 mg/kg every 3 weeks, overall tumour response rate by independent review was 43.8% with 6.3% complete response. All tumour responses were durable for > 18 weeks. In this study, 16 of the 35 MCD patients were hyaline vascular subtype; 31% of these patients had a radiologic response based on independent review and 88% showed clinical benefit response as defined in the protocol.

Study 3

An open-label, multicentre, non-randomised Phase 2 study assessed the safety and efficacy of extended treatment with siltuximab in 60 patients with MCD who were previously enrolled in Study 1 (41 patients) or Study 2 (19 patients). Median duration of siltuximab treatment was 5.52 years (range: 0.8 to 10.8 years); more than 50% of patients received siltuximab treatment for ≥5 years. After a median of 6 years of

follow-up, none of the 60 patients had died and maintenance of disease control was demonstrated in 58 of 60 patients.

Highest total dose in clinical trials

The highest total amount of siltuximab administered in any clinical trial so far per dose was 2,190 mg (11 mg/kg).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with siltuximab in all subsets of the paediatric population in CD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following the first administration of siltuximab (doses ranging from 0.9 to 15 mg/kg), the area under the concentration-time curve (AUC) and maximal serum concentration (C_{max}) increased in a dose-proportional manner and clearance (CL) was independent of dose. Following the single dose administration at the recommended dose regimen (11 mg/kg given once every 3 weeks), the clearance was 3.54 ± 0.44 mL/kg/day and half-life was 16.3 ± 4.2 days. Following the repeat dose administration at the recommended dose, siltuximab clearance was found to be time-invariant, and systemic accumulation was moderate (accumulation index of 1.7). Consistent with half-life after the first dose, serum concentrations reached steady-state levels by the sixth infusion (intervals every 3 weeks) with mean (± SD) peak and trough concentrations of 332 ± 139 and 84 ± 66 mcg/mL, respectively.

Immunogenicity

As with all therapeutic proteins, there is potential for the generation of anti-medicine 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 monotherapy and combination studies, samples from a total of 432 patients were available for anti-siltuximab antibody testing with 189 patients having at least one sample tested with the high medicinal product-tolerant ECLIA assay. The incidence rate of detectable anti-siltuximab antibodies was 0.9% (4/432) overall and 2.1% (4/189) in patients with at least once sample tested with the high medicinal product tolerant ECLIA assay. Further immunogenicity analyses were conducted for all positive samples from the 4 patients with detectable anti-siltuximab antibodies. None of these patients had neutralising antibodies. No evidence of altered safety or efficacy was identified in the patients who developed antibodies to siltuximab.

Special populations

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

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

Elderly

The population PK of siltuximab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the PK of siltuximab in patients older than 65 years compared to patients age 65 years or younger.

Renal impairment

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

Hepatic impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of siltuximab has been conducted. For patients with baseline alanine transaminase up to 3.7 times the upper limit of normal baseline albumin ranging from 15 to 58 g/L, and baseline bilirubin ranging from 1.7 to 42.8 mg/dL there was no meaningful effect on siltuximab PK.

Paediatric population

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

5.3 Preclinical safety data

The repeat-dose toxicology studies conducted in young cynomolgus monkeys at doses of 9.2 and 46 mg/kg/week (up to 22-fold greater exposure than in patients receiving 11 mg/kg every 3 weeks) with siltuximab showed no signs indicative of toxicity. A slight reduction in T-cell dependent antibody response and a reduction in the size of the splenic germinal centers following Keyhole limpet hemocyanin (KLH)

immunisation was observed which were considered to be pharmacological responses of IL-6 inhibition and not of toxicological significance.

Siltuximab (9.2 and 46 mg/kg/week) did not produce any toxicity of the reproductive tract in cynomolgus monkeys. In mice dosed subcutaneously with an anti-mouse IL-6 monoclonal antibody, no effects on male or female fertility were observed.

During an embryo-fetal development study where siltuximab was administered intravenously to pregnant cynomolgus monkeys (gestation day 20 – 118) at doses of 9.2 and 46 mg/kg/week, no maternal or fetal toxicity was observed. Siltuximab crossed the placenta during gestation whereby fetal serum concentrations of siltuximab at gestation day (GD) 140 were similar to maternal concentrations. Histopathological examination of lymphoid tissues from GD140 fetuses showed no morphological abnormalities in the development of the immune system.

Rodent carcinogenicity studies have not been conducted with siltuximab. Evidence from studies conducted with siltuximab and other IL-6 inhibitors suggest that the potential for siltuximab to cause carcinogenicity is low. However, there is also evidence to suggest that IL-6 inhibition may suppress immune responses, immune surveillance and lower defense against established tumours. Therefore, an increased susceptibility to specific tumours cannot be entirely ruled out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Histidine hydrochloride monohydrate

Polysorbate 80

Sucrose

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

4 years

After reconstitution and dilution

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

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

8 mL Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 100 mg of siltuximab. Pack size of 1 vial.

6.6 Special precautions for disposal

This medicinal product is for single use only.

- Use aseptic technique.

- Calculate the dose, total volume of reconstituted SYLVANT solution required and the number of vials needed. The recommended needle for preparation is 21-gauge 1½ inch (38 mm). Infusion bags (250 mL) must contain dextrose 5% and must be made of polyvinyl chloride (PVC), or polyolefin (PO), or polypropylene (PP), or polyethylene (PE). Alternatively PE bottles may be used.
- Allow vial(s) of SYLVANT to come to room temperature (15°C to 25°C) over approximately 30 minutes. SYLVANT should remain at room temperature for the duration of the preparation.

  Each 100 mg vial should be reconstituted with 5.2 mL of single-use water for injections to yield a 20 mg/mL solution.

- Gently swirl (DO NOT SHAKE OR VORTEX OR SWIRL VIGOROUSLY) the reconstituted vials to aid the dissolution of the powder. Do not remove contents until all of the powder has been completely dissolved. The powder should dissolve in less than 60 minutes. Inspect the vials for particulate matter and discolouration prior to dose preparation. Do not use if visibly opaque or if foreign particles and/or solution discolouration are present.
- Dilute the total volume of the reconstituted solution dose to 250 mL with sterile dextrose 5%, by withdrawing a volume equal to the volume of reconstituted SYLVANT from the dextrose 5%, 250 mL bag. Slowly add the total volume of reconstituted SYLVANT solution to the 250 mL infusion bag. Gently mix.
- The reconstituted solution should be kept for no more than 2 hours prior to addition into the intravenous 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 re-use.
- No physical biochemical compatibility studies have been conducted to evaluate the co-administration of SYLVANT with other medicinal products. Do not infuse SYLVANT concomitantly in the same intravenous line with other agents.
- Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Breakspear way,
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 44185/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

25/07/2024