

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125496Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 30, 2014

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Division of Risk Management

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Siltuximab (Sylvant)

Therapeutic Class: Chimeric monoclonal antibody against Interleukin-6

Dosage and Route: 11 mg/kg intravenous infusion every 3 weeks

Application Type/Number: BLA 125496

Applicant/sponsor: Janssen Biotech, Inc.

OSE RCM #: 2013-2131

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity siltuximab. On August 30, 2013, the Agency received an original Biologics License Application (BLA) from Janssen Biotech for siltuximab for the treatment of patients with multicentric Castleman's disease who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative. The applicant did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND^{1,2,3}

Castleman's disease is a rare, heterogeneous, atypical lymphoproliferative disorder associated with a range of clinical syndromes and histopathologic findings. The disease presents as either localized or multicentric disease and is characterized by changes in lymph node architecture that include germinal center hyperplasia, an accumulation of immunoblasts and plasma cells, and increased nodal vascularity. The multicentric type of Castleman's disease (MCD) is associated with HIV and HHV-8 infection, but MCD also occurs in the absence of these viral infections; the immune stimulus for viral-negative disease has not been identified. Both localized Castleman's disease and multicentric disease are linked with excessive secretion of interleukin-6 (IL-6), which acts as a potent growth factor for lymphocytes and plasma cells, and is believed to play a central role in the pathogenesis of the disease.

The clinical findings and prognosis of Castleman's disease vary according to the disease type. Most patients with localized disease are asymptomatic and the disease is usually curable with surgical resection of the affected lymph nodes. In contrast, patients with multicentric disease, which presents at a median age between 52 and 65, have generalized peripheral lymphadenopathy, hepatosplenomegaly, fevers, night sweats, edema and effusions, weight loss, fatigue, and other symptoms. Laboratory abnormalities such as anemia, thrombocytopenia, hypoalbuminemia, and hypergammaglobulinemia are also typical. The clinical course of MCD varies and includes indolent disease without worsening, episodic relapsing disease with recurrent exacerbations, and rapidly progressive disease that is often fatal. In addition to HIV and HHV-8, a number of malignancies and related conditions are associated with MCD, such as non-Hodgkin lymphoma, Kaposi sarcoma, Hodgkin lymphoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome.

There is no therapy currently approved in the U.S. for the treatment of Castleman's disease. Patients with multicentric disease usually require systemic therapy, and treatments commonly used for lymphoproliferative malignancies have been utilized. A number of therapeutic options are available, including corticosteroids, cytotoxic chemotherapy as single agents and in combination, and the CD-20 targeted monoclonal antibody rituximab. Treatment regimen decisions with these agents are often based on how aggressive the patient's disease appears to be as well as the patient's performance status.

¹ Dham A and Peterson BA. Castleman disease. *Curr Opin Hematol* 2007;14:354-359.

² Van Rhee F, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. *J Clin Oncol* 2010;28:3701-3708.

³ Aster JC and Brown JR. Castleman's disease. In: *UpToDate*, Freedman AS (Ed), UpToDate, Waltham MA, 2013.

Siltuximab is a recombinant chimeric monoclonal antibody that binds with high affinity and specificity to human IL-6 with the intent of neutralizing its biological activity and pathogenic role in MCD. Siltuximab does not bind to IL-6 produced by viruses.

1.2 REGULATORY HISTORY

On August 30, 2013, the Agency received an original Biologics License Application (BLA) for the use of siltuximab for the treatment of patients with multicentric Castleman's Disease who are HIV negative and HHV-8 negative. The applicant previously received orphan drug designation for the treatment of Castleman's disease on May 26, 2006. The review classification for the application is Priority. The sponsor did not submit a proposed REMS. A pharmacovigilance plan was submitted to the BLA on December 31, 2013 and will be reviewed by the Division of Pharmacovigilance under separate cover.

2 MATERIALS REVIEWED

- August 30, 2013, Original BLA 125496 submission. Sections reviewed include:
 - Section 1.14, Draft labeling
 - Section 2.5, Clinical Overview
 - Section 2.7.4, Summary of Clinical Safety
- October 22, 2013, slides from Janssen siltuximab BLA orientation meeting
- December 3, 2013, slides from BLA 125496 Mid-Cycle Meeting
- January 23, 2014, Draft Clinical Review BLA 125496

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The sponsor completed a Phase 2, randomized, double-blind, placebo-controlled, multi-center clinical study (MCD2001) in support of the proposed indication. The study population consisted of 79 adult patients with measurable, symptomatic disease who were HIV-negative and HHV-8-negative. Patients were randomized 2:1 to siltuximab (11 mg/kg IV every 3 weeks) plus best supportive care or placebo plus best supportive care. Treatment was continued until treatment failure, which was defined as disease progression based on symptoms, radiologic progression, or deterioration in performance status; other reasons for treatment discontinuation included adverse events, or other decisions made by the patient or physician. Patients treated with siltuximab received a median of 19 infusions compared to patients treated with placebo, who received a median of 8 infusions.

The primary efficacy endpoint for MCD2001 was a composite of durable tumor and symptomatic response sustained for at least 18 weeks as assessed by a central review committee. Major secondary efficacy endpoints included overall tumor response rate, time to treatment failure, increases in hemoglobin, and other endpoints. The primary efficacy endpoint showed a significant improvement in the siltuximab group compared with the placebo group, as 34% of siltuximab-treated patients experienced a durable response versus 0% of the placebo patients [95% CI of the difference (11.1, 54.8)]. Patients randomized to the siltuximab group also showed

significant treatment effects in tumor response rate, median time to treatment failure, and increases in hemoglobin compared with patients in the placebo group.

3.2 SAFETY CONCERNS

For the purpose of this review, severe adverse events associated with siltuximab are defined as Grade 3-5 in the NCI Common Terminology Criteria for Adverse Events.

3.2.1 Serious Adverse Events

Nonfatal serious adverse events (SAEs) of any nature were reported in 3/26 patients (12%) in the placebo group compared with 12/53 patients (23%) who received siltuximab. The most common nonfatal SAEs reported were related to infections, which occurred in five patients in the siltuximab group and two patients in the placebo group. Most other SAEs occurred in only one or two patients each in either group. One serious anaphylactic reaction was reported in a patient who received siltuximab therapy.

There were no deaths in Study MCD2001 related to siltuximab treatment. Two patients (4%) died due to disease progression after siltuximab had been discontinued. Four patients (15%) in the placebo group died; one of these patients developed pneumonia and congestive heart failure that led to death, whereas the others died due to disease progression or the development of myelodysplastic syndrome. One patient in a Phase 1 study of siltuximab MCD monotherapy died within 30 days of the last infusion due to sepsis. This patient had also received chemotherapy after disease progression.

3.2.2 Infusion-related reactions

Infusion-related reactions occurred in four patients randomized to siltuximab in Study MCD2001. Non-severe reactions occurred in three patients on the second, fourth and fifth infusions— one of these patients experienced reactions with two separate infusions that included pruritus, erythema, chest discomfort, or flushing. An additional patient developed a severe anaphylactic reaction (Grade 3) one day after the first infusion. The patient was hospitalized and treated, and siltuximab treatment was discontinued; the patient recovered on Study Day 16. In a separate clinical study of siltuximab for the treatment of myelodysplastic syndrome, a patient developed a severe infusion reaction with pain, palpitations, and transient inability to move his legs after receiving the second infusion. No treatment was needed and the events resolved the same day.

3.2.3 Hematologic toxicity

Patients treated with siltuximab experienced a higher incidence of Grade 1-2 neutropenia (30% versus 12%) and Grade 1-2 thrombocytopenia (23% versus 12%) compared with placebo. Severe adverse hematologic events (neutropenia, thrombocytopenia, or anemia) occurred in five patients in each group.

3.2.4 Infections

The incidence of infection of any grade was higher in siltuximab-treated patients compared with placebo-treated patients (66% versus 35%). Upper respiratory tract infections accounted for most

of the difference in incidence. There were six severe infections in the siltuximab group and three severe infections in the placebo group; two of the severe infections in each group were lower respiratory tract infections. There were no cases of tuberculosis, hepatitis B, or hepatitis C, though patients with hepatitis B surface antigen positivity or known hepatitis C infection were excluded from the clinical study.

3.2.5 Postmarketing Requirements

The applicant will be required to submit the final results from Study MCD2002, an open-label, multicenter study to evaluate the safety of long-term siltuximab treatment in patients with MCD.

4 DISCUSSION

Siltuximab is a recombinant monoclonal antibody directed against IL-6 and is proposed for use in the treatment of patients with multicentric Castleman's disease who are HIV-negative and HHV-8-negative. Multicentric Castleman's disease is a serious disease that can result in debilitating symptoms and fatal outcomes. In the pivotal clinical study (MCD2001), 34% of siltuximab-treated patients experienced a durable tumor and symptomatic response compared with 0% of the placebo patients. Secondary efficacy findings supported the improvement seen in durable response.

The most important safety concerns associated with siltuximab are infections and infusion reactions; non-severe hematologic adverse events also occurred at a higher incidence in siltuximab-treated patients. However, a significant difference in treatment exposure between the siltuximab group and placebo group makes comparison of the adverse event rates in this review somewhat unreliable. Infusion-related reactions were reported infrequently and generally did not result in serious outcomes or severe clinical manifestations; one patient experienced a serious, Grade 3 infusion reaction (reported as anaphylaxis) that occurred one day after the initial infusion. Infections were the most commonly reported adverse event. Serious infections in the siltuximab group included respiratory infections, sepsis, and an abscess. Although there was a higher overall incidence of neutropenia and thrombocytopenia observed in siltuximab-treated patients compared with placebo, each group reported the same number of severe adverse events. The current draft labeling includes warnings for infections, (b) (4), infusion reactions, and vaccinations; patients undergoing siltuximab treatment should not receive live vaccinations because IL-6 inhibition may interfere with the normal immune response to new antigens.

The pharmacologic class of monoclonal antibodies that inhibit IL-6 includes tocilizumab, which is a humanized monoclonal antibody with a similar mechanism of action as siltuximab. Tocilizumab binds the human IL-6 receptor, whereas siltuximab binds human IL-6. Tocilizumab is approved in Japan for the treatment of MCD. In the U.S., tocilizumab is approved with a REMS for the treatment of moderate to severe rheumatoid arthritis in adults who have not responded to disease-modifying drugs, and for the treatment of active juvenile idiopathic arthritis. The tocilizumab REMS is a communication plan to inform healthcare providers about the serious risks associated with the drug and is targeted to a broad range of adult and pediatric healthcare providers. A high-level comparison of the safety profiles of siltuximab and tocilizumab is found in the Appendix.

A number of factors are considered in determining if a REMS is necessary for siltuximab to ensure the benefits outweigh the risks for the treatment of MCD. Multicentric Castleman's disease is a rare lymphoproliferative disease with an unknown prevalence. Orphanet has estimated the prevalence of Castleman's disease to be less than 1/100,000.⁴ Using this estimate, the U.S. patient population is no more than a few thousand patients. MCD is a serious disease with debilitating symptoms. Left untreated, the disease is often fatal in association with fulminant infections, disease progression, and related malignancies, and there are no treatments currently approved in the U.S. Siltuximab is an effective treatment for MCD. Patients demonstrated clinically significant durable responses and will continue siltuximab as chronic therapy based on their clinical response and tolerance of the treatment. Most of the risks associated with siltuximab are also complications associated with the underlying disease.

DRISK does not recommend a REMS for management of the risks associated with siltuximab. Although tocilizumab has a similar mechanism of action and is approved with a REMS for serious risks associated with the treatment of several rheumatoid arthritis indications, the benefit-risk profile in the rheumatoid arthritis patient population is different compared with that for the MCD patient population. Multicentric Castleman's disease can rapidly progress into a life-threatening condition. There is a high background incidence of most of the adverse events associated with siltuximab that are also complications of the underlying disease, and the adverse events observed with siltuximab treatment did not seem more severe than complications of the disease itself. In addition, the likely prescribing population is comprised of hematologists and oncologists who treat hematological disorders and these providers are inherently informed and knowledgeable about managing the risks associated with siltuximab based on their experience in managing the disease state.

5 CONCLUSION

DRISK concurs with the Division of Hematology Products that, based on the available data and the potential benefits and risks of treatment, a REMS is not necessary for siltuximab and the risks associated with the product can be managed with the labeling. If new safety information becomes available, this decision can be re-evaluated.

⁴ Orphanet. The portal for rare diseases and orphan drugs. Castleman's disease. November 2006 (accessible at: http://www.orphanet.com/consortium/cgi-bin/OC_Exp.php?Expert=160&lng=EN).

APPENDIX

Table 1: Comparison of monoclonal antibodies that inhibit Interleukin-6

	Siltuximab	Tocilizumab
Description	Chimeric monoclonal antibody against IL-6	Humanized monoclonal antibody against IL-6 receptor
Indication(s)	<ul style="list-style-type: none"> ▪ Multicentric Castleman’s disease in HIV-negative and HHV-8-negative patients 	<ul style="list-style-type: none"> ▪ Adults with moderate to severe rheumatoid arthritis and an inadequate response to disease-modifying drugs ▪ Active polyarticular juvenile idiopathic arthritis ▪ Active systemic juvenile idiopathic arthritis
Boxed Warnings	None	<ul style="list-style-type: none"> ▪ Serious infections
Warnings and Precautions	<p>(Proposed)</p> <ul style="list-style-type: none"> ▪ Severe infections ▪ Vaccinations ▪ (b) (4) ▪ Infusion related reactions and hypersensitivity 	<ul style="list-style-type: none"> ▪ Serious infections ▪ Gastrointestinal perforations ▪ Laboratory parameters <ul style="list-style-type: none"> ○ Neutropenia ○ Thrombocytopenia ○ Elevated Liver Enzymes ○ Lipid Abnormalities ▪ Immunosuppression ▪ Hypersensitivity Reactions, including Anaphylaxis ▪ Demyelinating Disorders ▪ Active Hepatic Disease ▪ Vaccinations
Risk Management	Prescribing Information	REMS with communication plan

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01/30/2014

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