EMA/198014/2014

Summary of the risk management plan (RMP) for Sylvant (siltuximab)

This is a summary of the risk management plan (RMP) for Sylvant, which details the measures to be taken in order to ensure that Sylvant is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Sylvant, which can be found on Sylvant's EPAR page.

Overview of disease epidemiology

Castleman's disease is a rare disorder of the lymphatic system (the network of vessels that transport fluid from tissues through the lymph nodes and into the bloodstream) in which cells in lymph nodes start growing abnormally, causing benign tumours. The disease is called 'multicentric' when it affects several lymph nodes as well as other organs in the body. Patients have many general symptoms, including tiredness, fever, sweating at night, loss of appetite, peripheral neuropathy (nerve damage in the hands and feet causing tingling or numbness) and enlargement of the liver and spleen. Patients with multicentric Castleman's disease can have serious complications, such as problems with their immune system which make it difficult to fight infections, and lymphoma (a type of cancer).

Although the precise incidence of Castleman's disease is not known, it has been estimated at less than 1 in 100,000 people in Europe.

Summary of treatment benefits

Sylvant is used to treat multicentric Castleman's disease in adult patients who tested negative for the human immunodeficiency virus infection (HIV) and the human herpesvirus-8 (HHV-8). The active substance in Sylvant, siltuximab, is a monoclonal antibody (a type of protein) that has been designed to block the action of another protein in the body called interleukin-6 (IL-6), which is thought to contribute to the abnormal growth of certain cells in the lymph nodes. By blocking the activity of IL-6 Sylvant stops abnormal cell growth, thus decreasing the size of the lymph nodes and helping to reduce the symptoms of the disease.

Sylvant was compared with placebo (a dummy treatment) in one main study. This study involved 79 patients aged 18 years and older who were HIV-negative and HHV-8 negative. Patients in both groups also received other medicines to ease their symptoms. The main measure of how well Sylvant worked was the proportion of patients who responded to treatment for at least 18 weeks, as shown by a 50% reduction ('partial response') or complete disappearance ('complete response') of tumours and symptoms of the disease. Of 53 patients who received Sylvant, 17 showed a partial response and one showed a complete response, compared with none of the 26 patients who received placebo.

Unknowns relating to treatment benefits

There is no information in patients who have the localised form (in one lymph node, also called unicentric Castleman's disease) of the disease or in patients who are HIV-positive and/or HHV-8-positive. There is also no information about the use of Sylvant in children with multicentric Castleman's disease; however, the disease occurs very rarely in children.

Based on the results from the studies that were conducted to obtain marketing authorisation for Sylvant, there is no evidence to suggest that its effects would differ in different ethnic groups.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Decreased number of platelets (thrombocytopenia)	Thrombocytopenia is a very common side effect of treatment with Sylvant. Sylvant blocks IL-6 which may lead to a decrease in platelets, a type of blood cell involved in blood clotting. Risk factors include other medicines which may have an effect on the bone marrow where platelets are produced, and problems with the immune system that may produce antibodies that affect platelets.	A medical examination and blood test to count the number of platelets should be performed before each dose of Sylvant.
Decreased number of white blood cells (neutropenia)	Neutropenia is a very common side effect of Sylvant. Sylvant blocks IL-6, which may lead to a decrease in white blood cells, which are involved in fighting infections. Risk factors include certain other medicines and radiotherapy, which may affect the bone marrow where white blood cells are produced.	A medical examination and blood test to count the number of white cells should be performed before each dose of Sylvant.
Infusion reactions [infusion-related reactions and serious hypersensitivity (allergic) reactions]	Monoclonal antibodies such as Sylvant can cause infusion reactions. Symptoms include itching, redness of the skin, chest pain, and nausea (feeling sick). Infusion-related reactions and serious hypersensitivity (allergic) reactions are a common side effect during	If the patient experiences mild to moderate infusion reactions, administration of a medicine such as an antihistamine or lowering the rate of infusion may be considered. If the reaction is severe, treatment should be discontinued. Treatment for severe infusion reactions should be available at

Risk	What is known	Preventability
	treatment with Sylvant.	the institution where treatment with Sylvant is received.
High level of fats in blood [hyperlipidaemia (hypertriglyceridaemia and hypercholesterolaemia)]	Increased blood levels of fats called 'triglycerides' is a very common side effect with Sylvant; increased cholesterol levels is an uncommon side effect.	Blood levels of fats should be monitored, and life-style modifications should be made if needed.
High blood pressure (hypertension)	High blood pressure is a very common side effect with Sylvant.	Blood pressure should be monitored, and life-style modifications should be made if needed.
Reduced kidney function (renal impairment)	Impaired kidney function is a very common side effect with Sylvant.	Blood and urine tests should be performed, and life-style modifications should be made if needed.

Important potential risks

Risk	What is known
Liver damage	Increases in hepatic transaminases (liver enzymes) and bilirubin levels in the blood may occur in patients with Castleman's disease, including those treated with Sylvant. This may mean that the liver has been damaged.
Serious infections	Serious infections may develop in patients with Castleman's disease, including those treated with Sylvant. Sylvant blocks the protein IL-6; since IL-6 is also involved in fighting infections, blocking its effects may lead to infections and hide the signs of infection such as fever.
High levels of haemoglobin (the protein in red blood cells that carries oxygen around the body) and polycythaemia (increased number of red blood cells)	Sylvant blocks the protein IL-6, which may lead to an increase in haemoglobin above its normal levels. This is an uncommon side effect with Sylvant.
Cancer	Cancer (including lymphoma) may develop in patients with Castleman's disease, including in those treated with Sylvant. Blocking IL-6 may have an effect on the immune system, which could theoretically increase the risk of cancer.
Heart (cardiac) problems	Heart problems may occur in patients with Castleman's disease, including in those treated with Sylvant. Risk factors include high blood pressure, high levels of cholesterol in the blood, diabetes, smoking, age, male gender, being overweight, and a family history of cardiac

Risk	What is known
	problems.
Developing holes or tears in the stomach or bowel (gastrointestinal perforation)	Tears in the stomach or bowel may develop in patients with Castleman's disease, including those treated with Sylvant. Prevention includes a medical examination to see if a patient is at risk, for example having another disease that may increase the risk of this occurring.
Production of antibodies against Sylvant (immunogenicity)	The immune system may produce antibodies against Sylvant, which may cause a reaction during or after administration, or cause lack of effect of Sylvant. Prevention includes a medical examination to see if a patient is at risk, for example if the patient had a previous similar reaction after being treated with a monoclonal antibody.

Missing information

Risk	What is known
Use in pregnant or breastfeeding women	Sylvant has not been studied in pregnant or breastfeeding women. There is no information on the use of Sylvant in these patients, therefore Sylvant is not recommended in these patients.
Use in patients who are ≥65 years of age	Sylvant has been studied in very few patients over 65 years of age. There is limited information on the use of Sylvant in these patients.
Use in children	Sylvant has not been studied in children, as Castleman's disease occurs rarely in children. There is no information on the use of Sylvant in these patients.
Use in patients who are infected with the HIV virus	Sylvant has not been studied in patients who are infected with HIV.
Use in patients who are infected with human herpesvirus-8 (HHV-8)	Sylvant has not been studied in patients who are infected with HHV-8.
Use in patients who have received vaccines	Sylvant has not been studied in patients who received vaccines during treatment with Sylvant. Therefore, there is no information on the use of Sylvant in these patients.
Interaction between Sylvant and other medicines	In animal models, IL-6 is known to increase the activity of liver enzymes belonging to the CYP450 family, which are involved in breaking down medicines. In theory, binding of Sylvant to IL-6 could cause increased processing of medicines by CYP450 enzymes, which could make them less effective.

Risk	What is known
Use in patients with reduced liver function	Sylvant has not been studied in patients with reduced liver function. There is limited information on the use of Sylvant in these patients.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Sylvant can be found on Sylvant's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Registry: A multicentre registry for patients with Castleman's disease	The registry will collect information on patients with Castleman's disease. The registry will also assess how patients respond to treatment, how different treatments are chosen, how safe those treatments are.	Overall safety profile	Planned	Protocol: 31/12/2014 First tabulated update: 30/11/2015
Trials: CNTO328MCD2002 and CNTO328SMM2001	To assess whether patients develop antibodies against Sylvant (antibodies might stop Sylvant from	Extent of antibody production	Ongoing	CNTO328MCD2002: 4th quarter 2017 CNTO328SMM2001: 4th quarter 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	working properly or cause allergic reactions)			
Trial CNTO328MCD2002* An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Sylvant in Subjects with Multicentric Castleman's Disease	To assess the long-term safety of siltuximab in patients with multicentric Castleman's disease, how well Sylvant controls patients' disease, whether it has an effect on survival, to measure blood levels of IL-6 and to assess immunogenicity after long-term treatment with Sylvant.	Overall safety profile.	Ongoing	Final CSR: After 6-year data cutoff.
Trial: CNTO328MCD2001	To submit an updated analysis of overall survival.	Impact on survival	Ongoing	31 August 2017
Trial: CNTO328MCD2002	To submit an updated analysis of overall survival.	Impact on survival	Ongoing	31 August 2017

Studies which are a condition of the marketing authorisation

The updated analysis of overall survival for studies CNTO328MCD2001 and CNTO328MCD2002 and the multicentre registry for patients with Castleman's disease are conditions of the marketing authorisation for Sylvant.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 05-2014.