Drug Regulatory Affairs

Kevzara®

Summary of the Risk Management Plan (RMP) for Kevzara® (sarilumab)

Document version: 1.0

Document date: 27-Feb-2018

Based on EU-RMP v1.2 (Data lock point: 17-Feb-2016; Sign off date: 21-Apr-2017)

Marketing Autorisation Holder: sanofi-aventis (suisse) sa

SANOFI GENZYME REGENERON

Table of contents

TABLE OF CONTENTS 2

1) OVERVIEW 3

2) OVERVIEW OF DISEASE EPIDEMIOLOGY 4

3) SUMMARY OF TREATMENT BENEFITS 4

TABLE 1 - IMPORTANT IDENTIFIED RISKS 5

TABLE 2 - IMPORTANT POTENTIAL RISKS 6

TABLE 3 - MISSING INFORMATION 6

6) SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN 6

TABLE 4 - SUMMARY OF ADDITIONAL RISK MINIMIZATION ACTIVITIES BY SAFETY CONCERN 7

7) PLANNED POST AUTHORISATION DEVELOPMENT PLAN 8

TABLE 5 - ONGOING AND PLANNED STUDIES IN THE POST-AUTHORIZATION PHARMACOVIGILANCE DEVELOPMENT PLAN 8

8) STUDIES WHICH ARE A CONDITION OF THE MARKETING AUTHORISATION 8

9) SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME 8

TABLE 6 - SUMMARY OF CHANGES TO THE EU-RMP OVER TIME 8

Abbreviations

DLP:	Data Lock Point
DMARD:	Disease Modifying Anti-Rheumatic Drug
EU:	European Union
HIV:	Human Immunodeficiency Virus
INN:	International Nonproprietary Name
LDL:	Low Density Lipoprotein
MACE:	Major Adverse Cardiac Event
MTX:	Methotrexate
NSAID:	Non-Steroidal Anti-Inflammatory Drug
PL:	Patient Leaflet
RA:	Rheumatoid Arthritis
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
TB:	Tuberculosis

1) Overview

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.
The RMP summary of Kevzara® is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Kevzara® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of Kevzara®.

2) Overview of disease epidemiology

Rheumatoid arthritis (RA) is a chronic disease in which the immune system (which usually defends against infection) attacks healthy tissue, resulting in pain, swelling, and tenderness (inflammation) mainly in the small joints of the hands and feet; often accompanied by general feelings of tiredness or fatigue. Inflammation of the small joints can make it difficult to do daily tasks, and if untreated, can lead to irreversible destruction of joints and disability. Approximately 0.5% to 1% of the adult population in Europe is affected by Rheumatoid Arthritis.

3) Summary of treatment benefits

The efficacy and safety of sarilumab as a treatment for RA were evaluated in a comprehensive clinical program that included >3500 adult patients. Sarilumab treatment was assessed both in combination with commonly used conventional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), leflunomide, hydroxychloroquine, and sulfasalazine and when used alone as a monotherapy.
Study 1 (MOBILITY) included 1197 patients with RA who had not adequately improved while taking MTX, a commonly prescribed medication for RA. After 16 weeks patients treated with sarilumab (150 mg or 200 mg every 2 weeks) in combination with MTX had greater improvements in physical function and disability scores than patients who received MTX. After 24 weeks a greater percentage of patients treated with sarilumab in combination with MTX had decrease in swollen and tender joint counts and improvement in other signs and symptoms of RA compared to patients receiving MTX alone; these improvements were seen as early as 2 weeks after starting sarilumab. After 1 year, sarilumab in combination with MTX decreased the progression of joint damage compared to MTX alone. A greater percentage of patients in the sarilumab treatment groups had no worsening of joint damage on x-ray compared to the MTX group. Study 1 also showed that patients treated with sarilumab experienced greater improvement in physical aspects of general health, and greater reduction in self-reported fatigue.
Study 2 (TARGET) included 546 patients with RA who had an inadequate clinical response or were intolerant to one or more tumor necrosis factor blockers which are biologics prescribed for treatment of RA. Patients received sarilumab in combination with DMARDs during the study. Similar to results from Study 1, Study 2 showed that greater proportions of patients achieved improvement in signs and symptoms of RA and improvements in physical function scores for patients treated with sarilumab than patients who received placebo with DMARDs.
A long term follow up study of patients from Study 1 and Study 2 shows that the effectiveness of sarilumab 200 mg every 2 weeks continues 3 years after starting treatment.
Study 3 (MONARCH) included 369 patients with moderately to severely active RA who were inappropriate for treatment with MTX including those who were intolerant of or inadequate

responders to MTX. Patients in Study 3 received either sarilumab or adalimumab, a biologic prescribed for the treatment of RA, and were not allowed to use any other DMARD to treat RA during the study. In Study 3 reductions in disease activity of RA were greater for patients treated with sarilumab 200 mg than for patients treated with adalimumab 40 mg every 2 weeks for 24 weeks.
Results from these 3 studies show that treatment with sarilumab (200 mg or 150 mg every 2 weeks) is beneficial when used in combination with DMARDs or when used alone for the treatment of moderately to severely active RA in adult patients who responded inadequately or were intolerant to DMARDs or tumor necrosis factor blockers. Sarilumab inhibits progression of joint damage and improves signs and symptoms of RA and physical function in patients with moderately to severely active RA.

4) Unknowns relating to treatment benefits

Benefits of sarilumab for treatment of patients younger than 18 years or adult patients with other inflammatory disease have not been evaluated. Benefits of sarilumab for treatment of patients with RA have not been evaluated during pregnancy or breast-feeding.

5) Summary of safety concerns

Table 1 - Important identified risks

Risk	What is known	Preventability
Serious infections	Sarilumab can lower the ability of the immune system to fight infections. Some people have serious infections while taking sarilumab, including TB, and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.	Patients are informed in the Patient's Alert Card that to contact their HCP in an event of signs/symptoms of an infection
Hypersensitivity reactions	Hypersensitivity reactions (sometimes severe) have occurred in patients taking sarilumab. There have been a few reports of allergic reactions after sarilumab was given. These reactions were described as mild and moderate allergic reactions. In addition, there have also been rare cases of severe skin reactions in patients receiving sarilumab.	No preventative measure is anticipated.
Reduction in blood neutrophil counts (Neutropenia)	Low neutrophil counts were observed in the sarilumab clinical development program. A higher risk of infection was not seen in patients with low neutrophil counts.	Patients are informed in the Patient's Alert Card that white blood cell counts will be monitored during blood tests performed before and during the treatment
Tears (perforation) of the stomach or intestines (Gastrointestinal perforations)	Some people using sarilumab get tears in their stomach or intestine. This happens most often in people who also take NSAIDs, corticosteroids, or MTX.	Patients are instructed in the patient's Alert Card to contact their HCP in an event of signs/symptoms of Gastrointestinal perforations

TB: Tuberculosis. HCP: Healthcare Professional; NSAIDs: Non-Steroidal Anti-Inflammatory Drug; MTX: Methotrexate.

Table 2 - Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Reduction in blood platelets, which increases risk of bleeding or bruising (Thrombocytopenia and potential risk of bleeding)	Low blood platelet count was observed in patients who were enrolled in the sarilumab clinical development program. Decreased platelet count was not associated with bleeding.
Changes in liver enzymes with potential for liver damage (Clinically evident hepatic injury)	Changes in liver function tests were observed in the sarilumab clinical development program. There were no cases of drug-induced clinically significant liver damage.
Elevation of lipids and its effect on the heart and blood vessels (Lipid abnormalities and increased risk of major cardiovascular events)	Elevation of LDL was observed in the sarilumab clinical development program. Patients on sarilumab did not have an increased risk of heart attack or stroke.
Cancer (Malignancy)	Sarilumab may decrease the activity of immune system. Medicines that affect the immune system may increase the risk of certain cancers.

LDL: Low Density Lipoprotein.

Table 3 - Missing information

Risk	What is known
Use in pregnant and lactating women	Patients who became pregnant were not allowed to continue to receive sarilumab, therefore, there are very limited data about the use of sarilumab in pregnant women.
Use in pediatric patients	Sarilumab has not been evaluated in pediatric patients.
Use in elderly	There is limited data available in elderly patients.
Use in Hepatitis B/Hepatitis C infected patients	Sarilumab has not been evaluated in Hepatitis B/Hepatitis C infected patients
Use in HIV infected patients	Sarilumab has not been evaluated in HIV infected patients
Immunoglobulins levels following sarilumab treatment	No data available
Use of vaccination in patients receiving sarilumab	No data available

HIV: Human Immunodeficiency Virus.

6) Summary of risk minimisation measures by safety concern

All medicines have Information for Healthcare Professionals which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the information on the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the patient leaflet. The measures in these documents are known as routine risk minimization measures.
This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures).
These additional risk minimization measures are described below:

Table 4 - Summary of additional risk minimization activities by safety concern

Serious infections	
Risk minimization measure	Patient alert card
Objective and rationale	To remind both patients and healthcare providers involved in their treatment that the patient is being treated with sarilumab. To educate patients on the risk of serious infections. To remind patients to show the Patient Alert Card to doctors/HCPs involved with their medical care (especially in case of medical emergencies and/or if new Doctors/HCPs are involved).
Main additional risk minimization measures	Target audience: Patients In countries where the Patient Alert Card is used, it would be a credit-card size folded card carried by the patient. The prescribing HCP would be expected to fill-in their contact details and then give the card to the patient. Replacement Patient Alert Cards could be provided to patients by the HCPs.
Neutropenia	
Risk minimization measure	Patient alert card
Objective and rationale	To remind both patients and healthcare providers involved in their treatment that the patient is being treated with sarilumab. To educate patients on the risk of neutropenia. To remind patients to show the Patient Alert Card to doctors/HCPs involved with their medical care (especially in case of medical emergencies and/or if new Doctors/HCPs are involved).
Main additional risk minimization measures	Target audience: Patients In countries where the Patient Alert Card is used, it would be a credit-card size folded card carried by the patient. The prescribing HCP would be expected to fill-in their contact details and then give the card to the patient. Replacement Patient Alert Cards could be provided to patients by the HCPs.
Gastrointestinal perforations	
Risk minimization measure	Patient alert card
Objective and rationale	To remind both patients and healthcare providers involved in their treatment that the patient is being treated with sarilumab. To educate patients on the risk of gastrointestinal perforations. To remind patients to show the Patient Alert Card to doctors/HCPs involved with their medical care (especially in case of medical emergencies and/or if new Doctors/HCPs are involved).
Main additional risk minimization measures	Target audience: Patients In countries where the Patient Alert Card is used, it would be a credit-card size folded card carried by the patient. The prescribing HCP would be expected to fill-in their contact details and then give the card to the patient. Replacement Patient Alert Cards could be provided to patients by the HCPs.

PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

7) Planned post authorisation development plan

Table 5 - Ongoing and planned studies in the post-authorization pharmacovigilance development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Safety surveillance program using existing EU RA registries Cat.3	To evaluate the long-term safety of patients exposed to sarilumab in real-world clinical practice	Serious infections Lipid abnormalities and increased risk of major cardiovascular events Gastrointestinal perforations Malignancy Use in pregnant women	Planned	Protocol submitted on 18th Dec. 2017 1st interim report planned date: March 2019 Final report planned date: March 2027

EU: European Union

8) Studies which are a condition of the marketing authorisation

None of the studies in the previous section are a condition of the marketing authorization for Kevzara.

9) Summary of changes to the Risk Management Plan over time

Table 6 - Summary of changes to the EU-RMP over time

Version	Date	Safety concerns	Comment
1.0	09-Jun-2016	Not applicable as this is first version	-
1.1	15-Dec-2016		Based on D120 assessment, following changes have been made:
		Hypersensitivity reactions	Added as an important identified risk
		Increased risk of infection secondary to neutropenia	Renamed to Neutropenia and increased risk of infection
		Impact on cardiovascular outcome (MACE) secondary to LDL elevation	Renamed to Lipid abnormalities and increased risk of major cardiovascular events
		Clinical consequences of immunogenicity	Removed from important potential risks
		Use in elderly, Use in Hepatitis B/Hepatitis C infected patients, Use in HIV infected patients, IgE data following sarilumab treatment, Use of vaccination in patients receiving sarilumab	Added as missing information

Version	Date	Safety concerns	Comment
1.2	15-Mar-2017 21-Apr-2017		Based on D180 assessment, following changes have been made: Healthcare professional education guide removed from the list of risk minimization measures Study to measure the effectiveness of minimization measures “knowledge and understanding survey in the EU HCPs and patients" removed North American Pregnancy registry reclassified from Category 3 to Category 4
		Use in pregnant and lactating women	
		Neutropenia and increased risk of infection Neutropenia	Renamed to Neutropenia and upgraded as important identified risk Added in the patient alert Card
		Gastrointestinal perforations	Upgraded as important identified risk and added in the patient alert Card
		IgE data following sarilumab treatment	Renamed to Immunoglobulins levels following sarilumab treatment

MACE: Major Adverse Cardiac Event; IgE: Immunoglobulin E.