Summary of the Risk Management Plan (RMP) for ENJAYMO®

ENJAYMO® (Sutimlimab)
Marketing Autorisation Holder : sanofi-aventis (suisse) sa
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Disclaimer:

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 ENJAYMO® 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 ENJAYMO® 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 ENJAYMO®.

I.THE MEDICINE AND WHAT IT IS USED FOR

According to Swiss label

Sutimlimab is indicated for treatment of hemolysis in adult patients with cold agglutinin disease.

According to EU SmPC

ENJAYMO is authorized for treatment of hemolytic anemia in adult patients with cold agglutinin disease (CAD) (see SmPC for the full indication). It contains sutimlimab as the active substance and it is given by intravenous (IV) route.

II.RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ENJAYMO, together with measures to minimize such risks and the proposed studies for learning more about ENJAYMO's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet (PL) and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of ENJAYMO, routine risk minimization measures are supplemented with additional risk minimization measures (aRMMs) mentioned under relevant important risks, outlined in the next sections.

In addition to the risk minimization measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of important risks and missing information

Important risks of ENJAYMO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ENJAYMO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this

association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 26 - List of important risks and missing information

Important identified risk	Serious infections
Important potential risks	Meningococcal infections Development of Systemic Lupus Erythematosus Serious hypersensitivity reactions and/or anaphylaxis
Missing information	None

II.B. Summary of important risks

Table 27 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious infections

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Mechanism of action, class effect seen with terminal complement inhibitors and literature findings in subjects with acquired or inherited classical complement deficiency. The CP has multiple roles in both innate and adaptive immunity. Pharmacologic inhibition or inherited deficiency of the CP may lead to impaired opsonization of antigen antibody complexes, phagocytosis and pathogen neutralization or killing. (1)(2) While the CP plays an essential role for bacterial killing, particularly gram negative or encapsulated organisms, complement activation also occurs with other pathogens, such as viruses. (3)
Risk factors and risk groups	Risk factors for serious infections may include: patients that are unvaccinated or incompletely vaccinated; exposure to other immunomodulatory agents; concurrent hematologic and/or solid organ malignancies; other inherited or acquired immunodeficiency; asplenia; HIV/AIDS; CSF leak; cochlear implants; poorly controlled diabetes; chronic liver, kidney, heart, lung disease; elderly.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections: 4.2, 4.4 and 4.8 PIL sections: 2 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** • Physician's Guide • Patient's Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Cold Agglutinin Disease Real World Evidence Registry (Cadence) • A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

AIDS: Acquired Immuno Deficiency Syndrome; CSF: Cerebrospinal Fluid; CP: Classical Complement Pathway; HIV: Human Immunodeficiency Virus; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 28 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Meningococcal infections

Important potential risk: Meningococcal infections	
Evidence for linking the risk to the medicine	Mechanism of action, class effect seen with terminal complement inhibitors and literature findings in subjects with acquired or inherited classical and terminal complement deficiency. The complement system is part of our innate immunity and consists of three pathways (classical, lectin and alternative). The complement system has multiples roles in both innate and adaptive immunity. Pharmacologic inhibition or inherited deficiency of the components of the complement pathway may lead to impaired opsonization of antigen antibody complexes, phagocytosis and pathogen neutralization or killing. Terminal complement inhibition may prevent the formation of the membrane attack complex which is integral to the killing of *N. meningitidis*. (1)(2)
Risk factors and risk groups	Risk factors for meningococcal infections may include: patients that are unvaccinated or incompletely vaccinated against meningococcus, including serogroup B; exposure to terminal complement inhibitor therapies; other inherited or acquired immunodeficiency; asplenia; elderly.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections: 4.2 and 4.4 PIL sections: 2 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** • Physician's Guide • Patient's Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Cold Agglutinin Disease Real World Evidence Registry (Cadence) • A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 29 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Development of Systemic Lupus Erythematosus

Important potential risk: Development of Systemic Lupus Erythematosus	
Evidence for linking the risk to the medicine	Mechanism of action and literature findings in subjects with acquired or inherited classical complement deficiency. Long-term CP inhibition could theoretically increase the risk of SLE due to the role of the C1 complex in immune complex clearance, as seen in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). C4 and C1q deficiency identified as the strongest genetic risk factors for SLE. (4)(5)

Risk factors and risk groups	Patients that have concurrent autoimmune disease, pre-existing autoantibodies.
Risk minimization measures	**Routine risk minimization measures:** SmPC section: 4.4 PIL section: 2 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Cold Agglutinin Disease Real World Evidence Registry (Cadence)

C1: Complement component 1; C1q: Complement component 1, q subcomponent; C1r: Complement component 1, r subcomponent; C1s: Complement component 1, s subcomponent; C4: Complement component 4; CP: Classical Complement Pathway; PIL: Patient Information Leaflet; SLE: Systemic Lupus Erythematosus; SmPC: Summary of Product Characteristics.

Table 30 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious hypersensitivity reactions and/or anaphylaxis

Important potential risk: Serious hypersensitivity reactions and/or anaphylaxis	
Evidence for linking the risk to the medicine	Class effect with mAbs (literature); mechanism of action. Large protein molecules, despite humanization, can be immunogenic. Sutimlimab is biologic therapeutic protein and hypersensitivity risk, including anaphylaxis, is considered a class effect with mAbs. Serious hypersensitivity reactions, including anaphylaxis, have been observed with other mAbs. Inhibition of CP doesn't prevent LP or AP activation, which may produce potent anaphylatoxins.
Risk factors and risk groups	History of prior allergic reaction to sutimlimab and/or its excipients; Atopic individuals.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections: 4.2, 4.3 and 4.4 PIL sections: 2, 3 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Cold Agglutinin Disease Real World Evidence Registry (Cadence)

AP: Alternative Pathway; CP: Classical Complement Pathway; LP: Lectin Pathway; mAb: Monoclonal Antibody; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

II.C. Post-authorisation development plan

II.C.1 *Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of ENJAYMO.

II.C.2 ***Other studies in post-authorisation development plan***

Table 31 - Other studies in post-authorization development plan

Cold Agglutinin Disease Real World Evidence Registry (Cadence)
Purpose of the study: A disease registry that will be used to conduct a post-authorization safety study to describe the long-term safety and effectiveness of sutimlimab in patients with CAD in a real-word setting (including CAS patients in case of off-label use).
A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide
Purpose of the study: The overall goal of this study is to perform an effectiveness evaluation of the sutimlimab Physician's Guide among physicians who treat patients with CAD.

CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome.

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