swissmedic

*Date:* 23 April 2025
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*

# Enjaymo

| | |
|---|---|
| **International non-proprietary name:** | sutimlimab |
| **Pharmaceutical form:** | solution for infusion |
| **Dosage strength(s):** | 1100 mg/22 mL |
| **Route(s) of administration:** | intravenous use |
| **Marketing authorisation holder:** | Sanofi-Aventis (Suisse) SA |
| **Marketing authorisation no.:** | 68074 |
| **Decision and decision date:** | approved on 21 June 2023 |

**Note:**

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADCC | Antibody-dependent cell-mediated cytotoxicity |
| ADME | Absorption, distribution, metabolism, elimination |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| $AUC_{0\text{-}24h}$ | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| C1s | Complement protein component 1, s subcomponent |
| CAD | Cold agglutinin disease |
| CDC | Complement-dependent cytotoxicity |
| CE-SDS | Capillary electrophoresis-sodium dodecyl sulfate |
| CEX | Cation exchange |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CIC | Circulating immune complexes |
| CL | Clearance |
| $C_{max}$ | Maximum observed plasma/serum concentration of drug |
| CP | Complement pathway |
| CYP | Cytochrome P450 |
| DAT | Direct antiglobulin test |
| DDI | Drug-drug interaction |
| EMA | European Medicines Agency |
| ENA | Extractable nuclear antigen |
| EOT | End of treatment |
| ERA | Environmental risk assessment |
| FDA | Food and Drug Administration (USA) |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| Hb | haemoglobin |
| HLA | Human leukocyte antigen |
| HPLC | High-performance liquid chromatography |
| $IC/EC_{50}$ | Half-maximal inhibitory/effective concentration |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International non-proprietary name |
| ITT | Intention-to-treat |
| Kd | Dissociation constant |
| LoQ | List of Questions |
| MAH | Marketing authorisation holder |
| Max | Maximum |
| Min | Minimum |
| MRHD | Maximum recommended human dose |
| N/A | Not applicable |
| NO(A)EL | No observed (adverse) effect level |
| PBPK | Physiology-based pharmacokinetics |
| PD | Pharmacodynamics |
| PIP | Paediatric investigation plan (EMA) |
| PK | Pharmacokinetics |
| PopPK | Population pharmacokinetics |

| | |
|---|---|
| PSP | Pediatric study plan (US FDA) |
| RBC | Red blood cell |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SEC | Size-exclusion chromatography |
| SwissPAR | Swiss Public Assessment Report |
| t1/2 | Terminal half-life |
| TEAE | Treatment-emergent adverse event |
| Tmax | Time to maximum plasma concentration |
| TPA | Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21) |

# 2 Background information on the procedure

## 2.1 Applicant's request(s)

**New active substance status**
The applicant requested new active substance status for sutimlimab in the above-mentioned medicinal product.

**Orphan drug status**
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a$^{decies}$ no. 2 TPA.
Orphan drug status was granted on 15 October 2020.

## 2.2 Indication and dosage

### 2.2.1 Requested indication

Sutimlimab is intended for the treatment of haemolysis in adult patients with cold agglutinin disease (CAD).

### 2.2.2 Approved indication

Enjaymo is indicated for the treatment of haemolysis in adult patients with cold agglutinin disease (CAD) (see «Properties/Effects/Clinical Efficacy»).

### 2.2.3 Requested dosage

For patients weighing 39 kg to less than 75 kg, the recommended dose is 6500 mg and for patients weighing 75 kg or more, the recommended dose is 7500 mg. Enjaymo is intravenously administered weekly for the first two weeks, with administration every two weeks thereafter.

### 2.2.4 Approved dosage

(see appendix)

## 2.3 Regulatory history (milestones)

| | |
|---|---|
| Application | 30 November 2021 |
| Formal control completed | 30 December 2021 |
| List of Questions (LoQ) | 28 April 2022 |
| Response to LoQ | 26 July 2022 |
| Preliminary decision | 24 October 2022 |
| Response to preliminary decision | 22 December 2022 |
| Labelling corrections and/or other aspects | 1 March 2023 |
| Response to labelling corrections and/or other aspects | 30 March 2023 |
| Final decision | 21 June 2023 |
| Decision | approval |

# 3 Medical context

Cold agglutinin disease (CAD) is a rare, serious disease with chronic morbidities, with many patients experiencing potentially severe flares of haemolysis and anaemia. Patients with CAD have an increased risk of thromboembolic events and early mortality.

There are currently no approved therapies for the treatment of CAD in Switzerland. Current treatment options are supportive for symptomatic anaemia or disabling cold-induced circulatory symptoms. Therefore, there is an unmet medical need for an effective treatment.

# 4 Quality aspects

## 4.1 Drug substance

Sutimlimab, referred to as BIVV009, is a humanised IgG4 monoclonal antibody specific for C1s esterase. By binding to complement protein component 1, s subcomponent (C1s), BIVV009 blocks the classical complement pathway and prevents deposition of complement opsonins on the surface of red blood cells, resulting in inhibition of haemolysis in patients with cold agglutinin disease (CAD). Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities are not part of BIVV009's functionalities.
BIVV009 consists of two heavy and two kappa light chains connected by inter-chain disulfide bonds. The heavy chain has a carbohydrate moiety. BIVV009 is expressed in a Chinese hamster ovary (CHO) cell line and is manufactured using a fed-batch production process in a production bioreactor. The cell broth is harvested, and BIVV009 is subsequently purified by several chromatographic steps. The purification manufacturing process also contains dedicated viral clearance steps.
The fermentation and purification processes were validated and demonstrated a consistent manufacturing process that effectively reduces process-related impurities. The impurity clearance validation studies are supported by the impurity levels measured in the drug substance. The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity/impurity tests (e.g. size-exclusion chromatography (SEC), non reduced capillary electrophoresis-sodium dodecyl sulfate (non-reduced CE-SDS), cation exchange (CEX)), protein concentration and two biological activity assays. Batch analysis data from development, clinical, and process validation batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release. All the analytical methods are described, and the non-compendial methods were validated in accordance with ICH guidelines.
The drug substance is stored under appropriate storage conditions. No significant changes have been observed within the proposed shelf life.

## 4.2 Drug product

The finished product is a sterile, preservative-free, liquid dosage form intended for intravenous infusion. The finished product is used either undiluted with a nominal concentration of 50 mg/mL, or diluted with 0.9% Sodium Chloride Injection for concentrations < 50 mg/mL. The finished product is supplied as a single-dose vial containing 1100 mg of BIVV009 in 22 mL. The drug product is formulated in an aqueous buffered solution at pH 6.1, containing sodium phosphate, sodium chloride and polysorbate 80. All excipients comply with Pharmacopoeia quality requirements.

The selected manufacturing process consists mainly of drug substance pooling and mixing, sterile filtration, aseptic filling into vials, and stoppering followed by capping. Process validation studies were executed at commercial scale using several validation batches.
The specifications include relevant tests and limits, e.g. for appearance, pH, osmolality, particles, identity, biological activity assays, purity and impurity tests (SEC, non-reduced CE-SDS, CEX), protein and excipient concentration, sterility and bacterial endotoxins. All non-compendial methods were validated in accordance with ICH guidelines.
Batch analysis data for several batches from the commercial site are provided. The container closure systems in contact with the finished product consist of a glass vial with a chlorobutyl rubber stopper and an aluminium seal cap. All components coming into contact with the finished product comply with Ph. Eur. requirements.
The drug product is stored at 2-8°C. No meaningful changes have been observed under the proposed storage conditions. A shelf life of 36 months has been accepted.

## 4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product is supported by data from recommended storage conditions and by accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

# 5 Nonclinical aspects

## 5.1 Pharmacology

*In vitro* binding assays demonstrated that sutimlimab and its parental mouse monoclonal antibody TNT003 bind specifically to human C1s with high affinity (Kd 2.624 x $10^{-10}$ M and 2.616 x $10^{-10}$ M). Sutimlimab and TNT003 inhibited the classical pathway ($IC_{50}$ 0.34 and 0.21 µg/mL in 1% human serum) but not the alternative or lectin complement pathway. Sutimlimab and TNT003 bound to human and monkey C1s with similar high affinity. Both antibodies had low or no affinity to rat or mouse C1s. In the haemolytic activity potency assay, sutimlimab completely prevented human and cynomolgus monkey serum-mediated haemolysis ($IC_{50}$ 4.1 and 5.1 µg/mL in 20% serum), and exhibited partial activity in rat serum. However, the antibody was unable to prevent haemolysis in guinea pig, mini pig, dog, or rabbit serum. These data provide evidence that the cynomolgus monkey is an appropriate species to test the pharmacological and toxicological effects of sutimlimab. As sutimlimab and TNT003 displayed comparable pharmacological activity, *in vitro* proof of concept data obtained from studies with TNT003 were used to inform upon the pharmacology of sutimlimab. According to the submitted and published studies with samples from patients with cold agglutinin disease, immune thrombocytopenic purpura, or bullous pemphigoid, TNT003 inhibited complement fragment deposition on human red blood cells, platelets, and skin. In addition, TNT003 prevented complement-mediated tissue injury in transplant recipients by blocking human leukocyte antigen (HLA) antibody-triggered complement activation.
Since there is no adequate animal model to investigate the pharmacological effect of sutimlimab *in vivo*, the applicant conducted a pharmacodynamic (PD) analysis across the repeated-dose studies with cynomolgus monkeys. Once weekly intravenous administration of sutimlimab (up to 180 mg/kg) to cynomolgus monkeys induced dose- and time-dependent reduction of classical pathway activation. This reduction was observed as early as 5 minutes after the first dose at all dose levels (remaining activity 7-16.5%). The serum concentration of sutimlimab resulting in 90% inhibition of serum classical complement pathway (CP) activity ($IC_{90}$ value) was 22.3 µg/mL. Duration of inhibition was dose-dependent, and serum CP activity returned to the baseline level after 8 weeks of the recovery period. Sutimlimab binding was target-specific and showed no off-target binding to cognate serine proteases of the lectin pathway or C4 and C2 up to the concentration of 30 µg/mL (200 nM). Although this study was conducted at a concentration below the human pharmacologically active concentration, clinical data confirmed that sutimlimab is specific for C1s and does not inhibit other complement pathways. There were no sutimlimab-related effects on cardiovascular, respiratory, or neurological functions in the repeated-dose toxicology studies in cynomolgus monkeys at doses up to 180 mg/kg weekly (safety margins of 2.6 and 3.6 based on the exposure after 6.5 g and 7.5 g of human dose).

## 5.2 Pharmacokinetics

Single intravenous administration of 5-60 mg/kg of sutimlimab in cynomolgus monkeys showed a dose-proportional or more than dose-proportional increase in exposure (AUC and $C_{max}$). Increasing doses prolonged the terminal elimination ($t_{1/2}$ 4-59 h) and decreased clearance (CL).
In the repeated-dose studies (including an enhanced pre-/post-natal developmental (ePPND) study), exposure increased dose-proportionally or more than dose-proportionally at higher doses. CL and $t_{1/2}$ were dose-related, with rapid CL at low dose (target-mediated) and more stable at higher doses. $T_{1/2}$ increased (12.2-67.7h) with multiple doses of sutimlimab. There was no or only a negligible sex difference.
ADAs were detected in some animals across the studies and influenced the exposure to sutimlimab. Therefore, data from these animals were excluded from toxicokinetic analyses. Sutimlimab inhibited CP activity in a dose-dependent manner, with higher doses resulting in longer duration of inhibition. Sutimlimab was not measured in milk or infant serum. The recommendation that sutimlimab should

not be used during breastfeeding is considered adequate. Distribution, metabolism and excretion were not studied, which is in accordance with the ICH S6 (R1) guideline.

## 5.3 Toxicology

General toxicity and reproductive toxicity studies were conducted in immature cynomolgus monkeys, which were considered as a relevant species for the safety assessment based on the pharmacology data. Doses administered and dosing frequency ensured target saturation. The administration route was identical to the clinical route of administration. Two repeated-dose toxicity studies, 5- and 26-weeks including an 8-week recovery period at dose levels up to 100 and 180 mg/kg once weekly, were conducted. Sutimlimab treatment was well tolerated. There were no clinical signs, ophthalmic or neurological findings, or effects on body weight and food consumption, on haematology, clinical chemistry, or urinalysis parameters. Also, organ weights, and both macroscopic and microscopic investigations did not indicate a concern. The NOAEL was the highest dose level, representing safety margins of 2.6 and 3.6 at the clinical exposures after 6.5 g and 7.5 g, respectively.
Genotoxicity and carcinogenicity studies were not conducted, which is in line with the ICH S6(R1) guideline. Based on the weight of evidence approach that included a review of the currently published literature and the results of the nonclinical data, the risk for carcinogenicity in humans is considered low.
Regarding reproductive toxicity, the applicant did not provide a fertility study. No effects on male or female reproductive organs were observed in the repeated-dose studies. However, these animals were sexually immature. Therefore, the effect of sutimlimab on fertility remains unknown. In an ePPND toxicity study in monkeys, the intravenous administration of sutimlimab to pregnant monkeys during organogenesis at the maximum feasible doses (2 to 3 times the maximum recommended human dose), did not impact pregnancy, gestation length, maternal loss, or natural delivery. Sutimlimab did not cause maternal toxicity.
There were no sutimlimab-related effects in the infants in the developmental or behavioural parameters evaluated. Sutimlimab inhibited CP activity in maternal animals, but not in infant monkeys. No increase in autoimmunity markers (anti-dsDNA IgG, anti-ENA IgG and CIC-C1q) were observed across repeated-dose toxicity studies. Sutimlimab did not induce T cell proliferation in isolated human peripheral blood mononuclear cells. The investigators did not observe any findings at the injection site.
The summary of the key findings from the nonclinical studies in the RMP is considered adequate. There is no risk for the environment due to the protein nature of sutimlimab.

## 5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered appropriate to support the approval of sutimlimab in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered to be low but acceptable considering the indication. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

# 6 Clinical aspects

## 6.1 Pharmacokinetics

The pharmacokinetic characteristics were adequately described and are in line with expectations for a monoclonal antibody. Due to the dependence of the sutimlimab exposure on weight, a weight-based dosing is proposed, which is acceptable. The proposed dosing regimen ensures sufficiently high sutimlimab concentrations throughout the entire steady-state dosing interval.

## 6.2 Dosing

The applicant requested an undiluted administration of sutimlimab. However, most patients in the pivotal studies were treated with diluted sutimlimab. An undiluted administration of sutimlimab was only allowed for patients who were already treated with diluted sutimlimab (for at least 3 months in Part B) and who did not have a history of hypersensitivity to sutimlimab due to concerns of a possible increase in infusion-related reactions. The administration of undiluted sutimlimab was associated with a higher frequency of treatment-emergent adverse events (TEAEs) within 24 hours of infusion compared to diluted sutimlimab (39.1% vs. 26.1%). For details, please refer to the Information for healthcare professionals.

## 6.3 Clinical efficacy and safety

Evaluation of efficacy and safety of sutimlimab for the treatment of haemolysis in adult patients with CAD was based on the results of studies BIVV009-04 Part A (CADENZA study) and BIVV009-03 Part A (CARDINAL study). Following completion of a 6-month study period, patients received sutimlimab in an extension phase of these studies. For details regarding dosing please refer to the Information for healthcare professionals.

Both studies included patients aged ≥18 years with a confirmed diagnosis of primary CAD based on the following criteria: chronic haemolysis, polyspecific direct antiglobulin test (DAT) positive, monospecific DAT strongly positive for C3d, cold agglutinin titre ≥64 at 4˚C, IgG DAT ≤1+, and no overt malignant disease. For details regarding the included patient population please refer to the Information for healthcare professionals.

**CADENZA** is a randomised, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of sutimlimab in symptomatic patients with CAD who do not have a recent history of blood transfusion.

Following completion of dosing in the initial 6-month treatment period (Part A), patients continue to receive open-label sutimlimab for up to 1 year (Part B).

The primary endpoint in the controlled part of the study was a composite endpoint defined as meeting all 3 of the following criteria:

- Haemoglobin increased ≥1.5 g/dL from baseline (defined as the last haemoglobin value before administration of the first dose of IMP) at treatment assessment endpoint (defined as mean value from Weeks 23, 25, and 26) and
- The patient did not receive a blood transfusion from Week 5 through Week 26 (EOT), and
- The patient did not receive treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26 (EOT).

The study met the primary endpoint based on the proportion of patients who met all three primary endpoint criteria. The responder rate (all three composites reached) in the sutimlimab arm was 72.7% (16 patients) versus 15% (3 patients) in the placebo arm. The difference was statistically significant and clinically meaningful. However, the percentage of patients free of transfusion (81.8% vs. 80%) and the percentage of patients receiving no protocol-prohibited CAD medications from week 5 through week 26 (86.4% vs. 100%) were comparable to placebo. Furthermore, an improvement in fatigue for patients treated with sutimlimab was observed. For details, please refer to the Information for healthcare professionals.

The **CARDINAL** study was a single-arm, open-label trial that included 24 adult patients with primary CAD who had at least one blood transfusion in the previous 6 months, haemoglobin (Hb) ≤10g/dL and symptomatic disease. Following completion of dosing in the initial 6-month treatment period, patients continue to receive sutimlimab for up to 24 months.

The primary efficacy endpoint was responder rate, which was a composite endpoint. Patients were classified as a responder if they met the following criteria;

- The patient did not receive a blood transfusion from Week 5 through Week 26 (EOT),
- The patient did not receive treatment for CAD beyond what was permitted per protocol.
- Patient achieved an Hb level ≥ 12 g/dL or an increase in Hb ≥ 2 g/dL compared to baseline at the treatment endpoint (mean value from week 23, 25, and 26).

In total, 54.2% of patients met the composite primary endpoint criteria: 15 (62.5%) patients met the Hb endpoint, 17 (70.8%) patients were transfusion-free from weeks 5 to 26, and 22 (91.7%) patients did not receive protocol prohibited CAD medications.

The durability of response beyond 26 weeks was evaluated in Part B of the CADENZA/ CARDINAL studies. For Part B no formal statistical hypotheses were tested, and all efficacy analyses of Part B are descriptive. Discontinuation of sutimlimab and the resulting cessation of classical pathway (CP) inhibition led to a return of haemolysis activity, as evidenced by changes in laboratory markers of haemolysis, by an increase in transfusion requirements and by changes in fatigue scores approaching pre-treatment values. Only limited data, mainly from real world data from named patient programs, are available for re-treatment after cessation of therapy. Complement inhibition and control of haemolysis were rapidly restored when treatment was restarted.

Of concern is the effect of sutimlimab on circulatory symptoms. An influence of sutimlimab on the course of circulatory symptoms cannot be ruled out. Thromboembolic adverse events were observed in patients with CAD treated with sutimlimab. For details regarding this risk, please refer to the Information for healthcare professionals.

Safety:
In total, 76 patients with cold agglutinin disease (CAD) were included in the safety analysis. The size of the safety database is acceptable given the rarity of the disease. The most common TEAEs (≥20%) were respiratory tract infection, nasopharyngitis, arthralgia/arthritis, diarrhoea, headache and systemic hypertension. For details, please refer to the Information for healthcare professionals.

For evaluation of relevant safety risks such as thromboembolism and infections, longer follow-up data are necessary. Data from the registry (PMR FDA 3922-1) were requested as a condition.

## 6.4 Conclusion

In summary, the trial results indicate that sutimlimab confers substantial benefits in terms of a reduction in blood transfusions, an increase in haemoglobin levels, and reducing fatigue in patients with CAD. However, sutimlimab is not appropriate as therapy for circulatory symptoms of CAD. Cold-

induced circulatory symptoms are part of the disease caused by red blood cell (RBC) agglutination and are not reduced by complement blockade with sutimlimab. This is of particular relevance for patients for whom circulatory symptoms are the main indication for treatment.

The overall safety profile is acceptable and manageable for patients with CAD. However, it is expected that continuous lifelong therapy with sutimlimab would be required in the absence of definitive treatment of the underlying cause. Long-term safety results - in particular, for relevant toxicities such as infections and thromboembolic events - are limited.

The benefit-risk profile for sutimlimab is positive for the treatment of haemolysis in patients with CAD. Submission of results from the Cadence registry for the evaluation of long-term safety was requested as a condition.

# 7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

# 8 Appendix

## Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Enjaymo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. For advice on the reporting of adverse reactions, see the section “Undesirable effects”.

# Enjaymo ®

## Composition

*Active substances*

Sutimlimab*

* Sutimlimab is an immunoglobulin G4 (IgG4) monoclonal antibody manufactured from genetically modified Chinese Hamster Ovary (CHO) cells.

*Excipients*

Polysorbate 80, sodium chloride, sodium monohydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, water for injection

This medicinal product contains 76 mg of sodium per vial, equivalent to 3.85% of the maximum daily sodium intake with food of 2 g recommended by the WHO for adults.

## Pharmaceutical form and active substance quantity per unit

Solution for infusion
Opalescent, colourless to slightly yellowish solution free of preservatives and essentially free of visible particles, with a pH value of approx. 6.1 and an osmolality of 268-312 mOsm/kg.
1 ml solution for infusion contains 50 mg of sutimlimab.
Each vial contains 1,100 mg of sutimlimab in 22 ml (1,100 mg/22 ml).

## Indications/Uses

Enjaymo is indicated for the treatment of haemolysis in adult patients with cold agglutinin disease (*CAD*) (see “Properties/Effects/Clinical Efficacy”).

## Dosage/Administration

Enjaymo must be administered by a healthcare professional and under the supervision of a physician experienced in the treatment of patients with hematological disorders. In order to ensure the traceability of biotechnologically manufactured medicinal products, it is recommended to document the trade name and batch number with each treatment.

Patients should be vaccinated according to the current local recommendations for patients with persistent complement disorders (see section “Warnings and precautions”).
Patients without prior vaccination against encapsulated bacteria must be vaccinated at least two weeks prior to receiving the first dose of Enjaymo. If urgent Enjaymo therapy is indicated in an unvaccinated patient, administer vaccine(s) as soon as possible.

*Usual dosage*

The recommended dosage of Enjaymo for patients with cold agglutinin disease is based on body weight. For patients weighing 39 kg to less than 75 kg, the recommended dose is 6 500 mg and for patients weighing 75 kg or more, the recommended dose is 7 500 mg. Administer Enjaymo intravenously weekly for the first two weeks, with administration every two weeks thereafter Enjaymo should be administered at the recommended times of the dosage regimen time points, or within two days of these time points.
In the clinical studies, the administration of Enjaymo was limited to the study duration. Patients received Enjaymo for an additional 12 months (CADENZA) or 24 months (CARDINAL) after completion of a 6-month treatment period (Part A) in both studies as part of an extension phase (Part B) (see “Clinical efficacy”).

*Late dose administration*

If a dose is missed, the missed dose should be administered as soon as possible. If more than 17 days have elapsed since the last dose administration, the therapy should be reinitiated according to the schedule listed under “Dosage/Administration”.

*Mode of administration*

Enjaymo is intended for intravenous infusion only. Do not administer as an intravenous push or bolus. For instructions on preparation and administration, see section “Other information”.
Enjaymo can be used either as an undiluted or diluted preparation (for detailed information regarding the patient population, see also section “Warnings and precautions”). After preparation, the Enjaymo infusion should be administered intravenously at the infusion rate specified in Table 1 (undiluted) or Table 2 (diluted).

Table 1 – Reference table for infusions (undiluted)

| Body weight (range) | Dose (mg) | Number of Enjaymo vials needed | Volume of Enjaymo | Maximum infusion rate |
|---|---|---|---|---|
| Greater than or equal to 39 kg to less than 75 kg | 6,500 | 6 | 130 ml | 130 ml/hour* |
| 75 kg or more | 7,500 | 7 | 150 ml | 150 ml/hour* |

* Patients with cardiopulmonary disease may receive the infusion over 120 minutes.

Table 2 – Reference table for infusions (diluted in 0.9% sodium chloride solution)

| Body weight (range) | Dose (mg) | Number of Enjaymo vials needed | Volume of Enjaymo | Volume of the NaCl solution | Total volume | Maximum infusion rate |
|---|---|---|---|---|---|---|
| Greater than or equal to 39 kg to less than 70 kg | 6,500 | 6 | 130 ml | 370 ml | 500 ml | 250 ml/hour |
| 70 kg to less than 75 kg | 6,500 | 6 | 130 ml | 370 ml | 500 ml | 500 ml/hour |
| 75 kg or more | 7,500 | 7 | 150 ml | 350 ml | 500 ml | 500 ml/hour |

If hypersensitivity reactions occur, discontinue Enjaymo and initiate appropriate treatment. Monitor patients for at least two hours after completion of the first infusion for signs or symptoms of an infusion-related and/or hypersensitivity reaction. Monitor patients for one hour following completion of subsequent infusions for signs or symptoms of an infusion-related reaction.

*Elderly patients (> 65 years)*

No dose adjustment is required in patients with cold agglutinin disease aged 65 years and older. Of the 66 patients with cold agglutinin disease in clinical trials of Enjaymo, 65% (43/66) were 65 years of age or older, including 27% aged 75 years or older. No differences in response between patients over 65 years of age and younger patients are evident from the clinical experience reported.

*Children and adolescents*

The safety and efficacy in patients under 18 years of age have not been demonstrated.

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in the section “Composition”.

**Warnings and precautions**

*Serious infections*

Patients may be more susceptible to serious infections, particularly infections caused by encapsulated bacteria such as Neisseria meningitides, Streptococcus pneumoniae and Haemophilus influenzae.

In clinical studies on cold agglutinin disease, serious infections, including sepsis, respiratory tract infections and skin infections have been reported in patients who received Enjaymo (see section “Undesirable effects”). Enjaymo should not be used in patients with active, serious infections. Patients should be monitored for early signs and symptoms of infections and informed to seek immediate medical treatment if such symptoms occur.

If Enjaymo is administered to patients with active systemic infections, they should be closely monitored for signs and symptoms of worsening of the infection. Some infections can quickly take a life-threatening or fatal course if they are not detected and treated immediately. Patients should be

informed of these signs and symptoms and the steps they should take to seek immediate medical treatment. Interruption of treatment with Enjaymo should be considered in patients treated for a serious infection. Enjaymo has not been studied in patients with chronic systemic infections such as hepatitis B, hepatitis C or HIV. When starting treatment with Enjaymo, the immune status of the patients must be taken into account.

*Vaccinations*
Patients should be vaccinated according to current local recommendations for patients with persistent complement disorders, including meningococcal and streptococcal vaccines. Patients should be revaccinated according to local recommendations.

Patients without prior vaccination against encapsulated bacteria must be vaccinated at least two weeks before the first administration of Enjaymo. If treatment with Enjaymo is urgently indicated in an unvaccinated patient, the vaccine(s) must be given as soon as possible. Vaccination reduces, but does not eliminate, the risk of infections with encapsulated bacteria. The benefits and risks of antibiotic prophylaxis to prevent infections in patients receiving Enjaymo are not known.

*Hypersensitivity reactions*
Administration of Enjaymo may lead to hypersensitivity reactions, including anaphylaxis. In clinical studies, hypersensitivity reactions have occurred in patients receiving Enjaymo. If hypersensitivity reactions occur, Enjaymo should be discontinued, and appropriate treatment initiated (see section “Dosage/Administration”).

*Infusion-related reactions*
Administration of Enjaymo may result in infusion-related reactions during the infusion or immediately after the infusion (see section “Undesirable effects”). Patients should be monitored for infusion-related reactions, the infusion should be discontinued if a reaction occurs, and appropriate treatment initiated.

*Undiluted infusion*
Data from 23 (out of a total of 39) patients from Part B of the CADENZA study are available for the undiluted infusion. The undiluted solution was administered to patients who had been treated with Enjaymo for at least 3 months in Part B and had no history of hypersensitivity reactions to Enjaymo. The number of Treatment-Emergent Adverse Events (TEAEs) occurring within 24 hours after administration of the undiluted infusion was higher than the number of TEAEs occurring within 24 hours after administration of the diluted infusion (39.1% versus 26.1%). No TESAEs occurred within 24 hours of administration of the undiluted infusion. The non-serious events of hypertension and

erythema at the injection site occurred in 2 patients each within 24 hours of administration of undiluted infusion; none of these events led to a temporary interruption or discontinuation of Enjaymo treatment.

*Systemic lupus erythematosus*

Individuals with inherited classical complement pathway disorders have a higher risk of developing systemic lupus erythematosus (SLE). Based on its mechanism of action, Enjaymo may potentially increase the risk of developing autoimmune diseases such as SLE. Patients with SLE were excluded from the clinical studies with Enjaymo. Patients receiving Enjaymo should be monitored for signs and symptoms of SLE and examined accordingly. Caution should be exercised when using Enjaymo in patients with SLE or patients who develop signs and symptoms of SLE.

*Circulatory symptoms*

An influence of Enjaymo on the course of circulatory symptoms (such as acrocyanosis and Raynaud's phenomenon) cannot be excluded.

In CAD patients participating in clinical trials with Enjaymo, a total of 5 thromboembolic adverse effects (cerebral venous sinus thrombosis, device-related thrombosis, peripheral arterial thrombosis, transient ischaemic attack, and deep vein thrombosis). Cerebral venous sinus thrombosis and peripheral arterial thrombosis were reported as serious events; other events were reported as non-serious. Cerebral venous thrombosis occurred in the context of a meningioma and otomastoiditis. The event resolved two days after onset of treatment with oral antithrombotics.

*Monitoring for manifestations of cold agglutinin disease after discontinuation of Enjaymo*

The effects on hemolysis diminish a few weeks after the end of treatment. Patients should therefore be monitored for signs and symptoms of haemolysis identified by increased total bilirubin or LDH levels in conjunction with a decrease in haemoglobin levels or the recurrence of symptoms such as fatigue, dyspnoea, palpitations or haemoglobinuria, in the event of treatment discontinuation.

**Interactions**

No interaction studies were conducted.

**Pregnancy, lactation**

*Pregnancy*

There are no available data to date on Enjaymo from the use in pregnant women. There are no conclusions as to whether Enjaymo is safe for use during pregnancy. Animal studies did not reveal any indications of direct or indirect harmful health effects with regard to reproductive toxicity (see "Preclinical data" section).

It is known that human IgG antibodies can cross the placental barrier; thus, sutimlimab may be transmitted from the mother to the developing foetus.

For reasons of caution, use of Enjaymo during pregnancy should be avoided. Enjaymo should only be administered during pregnancy if clearly indicated.

*Lactation*

There are no data on the presence of sutimlimab in human milk, effects on milk production or the effects on the breast-fed child. Maternal IgG is known to occur in human milk. No conclusions can be drawn regarding whether Enjaymo is safe for use during breast-feeding. A decision must be made whether breast-feeding should be discontinued or to discontinue/abstain from Enjaymo therapy. Both the benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account.

*Fertility*

The effects of sutimlimab on male and female fertility have not been studied in animals.

**Effects on ability to drive and use machines**

Enjaymo has no or negligible effect on the ability to drive or use machines.

**Undesirable effects**

*Summary of the safety profile*

The safety of Enjaymo in patients with a confirmed diagnosis of cold agglutinin disease was investigated in a pooled population of a placebo-controlled study (CADENZA) and an open-label, single-arm study (CARDINAL) (n = 66) (see “Clinical efficacy”).
The most frequently reported adverse reactions that occurred in ≥ 15% of patients in the clinical studies of Enjaymo were hypertension, respiratory tract infection, headache, nasopharyngitis, infusion-related reactions, cyanosis (acrocyanosis), nausea and abdominal pain. Serious adverse reactions have been reported in 19.6% (13/66) of patients receiving Enjaymo. These serious adverse reactions were respiratory tract infection (n = 3), urinary tract infection (n = 3), viral infection (n = 2), cyanosis (n = 2), skin infection (n = 1), hypertension (n = 1), abdominal pain (n = 1), herpes infection (n = 1), Raynaud phenomenon (n = 1) and stress cardiomyopathy (n = 1). Adverse reactions led to discontinuation of Enjaymo in 6.1% (4/66) of patients. These were cyanosis (acrocyanosis) (n = 3), respiratory tract infection (n = 1), reaction associated with an infusion (n = 1) and Raynaud’s phenomenon (n = 1).

*List of undesirable effects*

In Table 3, the adverse reactions observed in the CADENZA and CARDINAL studies are listed by system organ class and frequency, using the following categories: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/10,000), very rare (< 1/10,000). Within each frequency category, the side effects are listed according to descending severity.

**Table 3 – List of side reactions observed in the CADENZA and CARDINAL studies**

| | Very common | Common |
|---|---|---|
| MedDRA system organ class | | |
| Infections and infestations | Urinary tract infection (28.8%)[a]<br>Respiratory tract infection (27.3%)[b]<br>Nasopharyngitis (21.2%)[c]<br>Herpes infection (10.6%)[d]<br>Gastroenteritis (10.6%)<br>Rhinitis (10.6%) | Viral infection[j]<br>Skin infection[g]<br>Tooth infection[i]<br>Eye infection[h]<br>Abdominal infection[k]<br>Vaginal infection<br>Bacterial infection |
| Psychiatric disorders | | Anxiety<br>Confusional state |
| Nervous system disorders | Headache (21.2%) | Aura*<br>Dizziness* |
| Vascular disorders | Hypertension (30.3%)[e]<br>Cyanosis (reported as acrocyanosis) (19.7%)<br>Raynaud's phenomenon (10.6%) | Hypotension*<br>Stress cardiomyopathy* |
| Respiratory, thoracic and mediastinal disorders | | Chest discomfort* |
| Gastrointestinal disorders | Abdominal pain (18.2%)[f]<br>Nausea (18.2%) | Vomiting<br>Diarrhoea*<br>Dyspepsia*<br>Aphthous ulcer* |
| Skin and subcutaneous tissue disorders | | Rash |
| General disorders and administration site conditions | | Erythema[l]<br>Pyrexia*<br>Feeling of cold*<br>Infusion-related reaction*<br>Pruritus[m] |

a. Urinary tract infection: Urinary tract infection, cystitis, Escherichia urinary tract infection, urinary tract infection bacterial, cystitis bacterial, urosepsis
b. Respiratory tract infection: Upper respiratory tract infection, respiratory tract infection, bronchitis, lower respiratory tract infection, respiratory tract infection viral, viral upper respiratory tract infection, pneumonia, Klebsiella pneumonia, COVID-19-Pneumonie
c. Nasopharyngitis: Nasopharyngitis, pharyngitis
d. Herpes infection: oral Herpes, Herpes Zoster, Herpes Simplex, Herpes Simplex Viremia
e. Hypertension: Hypertension, blood pressure increased, essential hypertension, hypertensive crisis, white coat hypertension
f. Abdominal pain: abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.
g. Skin infection: Skin infection, staphylococcal skin infection, wound infection staphylococcal, tinea infection, fungal skin infection, skin candida
h. Eye infection: Eye infection, eye infection bacterial
i. Tooth infection: Tooth infection, root canal infection
j. Viral infection: Viral infection, febrile infection, influenza, sinusitis
k. Abdominal infection: abdominal infection, infection
l. Erythema: including injection site erythema
m. Pruritus: including injection site pruritus

* Infusion related reaction: All occurred within 24 hours of the start of the Enjaymo infusion.

*Immunogenicity*

The immunogenicity of sutimlimab was assessed in patients with cold agglutinin disease in the CARDINAL and CADENZA studies at baseline, during the treatment period and at the end of treatment (week 26). Two of the 24 patients who were enrolled in the CARDINAL study and had received at least one dose of sutimlimab developed treatment-emergent antibodies against the drug (*anti-drug antibodies*, ADA). In the CADENZA study, 6 of the 42 patients treated with sutimlimab developed treatment-related ADAs. These ADAs were transient and with low titer and were not associated with changes in the pharmacokinetic profile, clinical response or adverse events.

*Reporting suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

**Overdose**

No cases of overdose have been reported in clinical studies.
In patients with overdose, immediate interruption of the infusion and close monitoring are recommended.

**Properties/Effects**

*ATC code*

L04AA55

*Mechanism of action*

Sutimlimab is a monoclonal antibody (mAb) of immunoglobulin class G (IgG), subclass 4 (IgG4), which inhibits the classical complement pathway and binds specifically to the s subcomponent (C1s) of complement protein component 1. C1s is a serine protease and cleaves C4. The activities of the lectin and the alternative activation pathways are not inhibited by sutimlimab. Inhibition of the classical complement pathway at the level of C1s prevents the deposition of the complement opsonines on the erythrocyte surface, which leads to inhibition of hemolysis in patients with cold agglutinin disease, prevents the formation of the pro-inflammatory anaphylatoxins C3a and C5a and the downstream terminal complement complex C5b-C9. Cold agglutinin disease is characterized by chronic hemolysis, caused by lysis of erythrocytes mediated by the classical complement pathway. Sutimlimab inhibits hemolysis in patients with cold agglutinin disease by inhibiting the classical complement pathway.

*Pharmacodynamics*

At the end of the first infusion of sutimlimab, an immediate and greater than 90% inhibition of the classical complement pathway was observed. This inhibition was maintained in all patients with cold

agglutinin disease who received sutimlimab in concentrations of more than 100 µg/ml over the entire 26-week treatment period. C4 levels returned to normal values (0.2 g/l) in patients with cold agglutinin disease within one week of the first administration of sutimlimab. Complete inhibition of the classical activation pathway after the start of treatment with sutimlimab led to rapid inhibition of hemolysis, which was demonstrated by normalisation of bilirubin levels, a decrease in LDH levels, an increase in haptoglobin values and a decrease in the reticulocyte count.
After the first treatment with sutimlimab, an almost complete normalisation of the bilirubin values was observed with a rapid increase of the hemoglobin level by > 1 g/dl, demonstrating the effect of inhibition of the classical activation pathway. The extent and duration of the pharmacodynamic response in patients with cold agglutinin disease depended on the exposure to sutimlimab.

*Clinical efficacy*

The safety and efficacy of Enjaymo in patients with cold agglutinin disease have been assessed in two six-month clinical studies:

- a placebo-controlled study in patients with cold agglutinin disease (CADENZA)
- a single-arm study in patients with cold agglutinin disease (CARDINAL).

Both studies included a 9-week follow-up after the last dose of Enjaymo.

Both studies included patients with a confirmed diagnosis of cold agglutinin disease based on chronic hemolysis, polyspecific direct antiglobulin test (DAT), monospecific DAT for C3d, cold agglutinin titre ≥ 64 at 4 °C and an IgG-DAT ≤ 1+. Patients with cold agglutinin disease secondary to infection, rheumatologic disease, systemic lupus erythematosus or active haematological malignancy were excluded from the studies. Patients with a history of known or existing low-grade lymphoproliferative concomitant disease were included in the studies.
The patients enrolled in the CARDINAL study had at least one documented blood transfusion within 6 months prior to study entry. The patients in the CADENZA study had no transfusion within 6 months, or more than one blood transfusion in the last 12 months prior to study enrolment.

*CADENZA study*
Forty-two (42) patients were randomly assigned to treatment with 6,500 mg or 7,500 mg of sutimlimab (depending on body weight) intravenously over approximately 60 minutes on day 0, day 7 and then every 14 days through week 25 (n = 22), or placebo (n = 20).
After completion of the 6-month treatment period (Part A), 39 patients (19 patients previously receiving Enjaymo and 20 patients previously receiving placebo) received Enjaymo for 12 months in an extension phase (Part B). The mean overall exposure to Enjaymo in Part A and B of the CADENZA study was 93 weeks. The max. exposure to Enjaymo in the extension phase (B) was 150 weeks.

The baseline characteristics and demographic data of the patients in the CADENZA study were comparable between the two treatment groups and included a mean age of 65.3 years (range: 46-88) and 68.2 years (range: 51-83) as well as a mean body weight of 66.8 kg (range: 39-100) and 64.9 kg (range: 48-95) in the Enjaymo and Placebo group respectively. 77.3% in the Enjaymo group and 80.0% in the placebo group were female. At baseline, the mean hemoglobin level was 9.15 g/dl in the Enjaymo group and 9.33 g/dl in the placebo group and the mean total bilirubin value was 41.17 µmol/l (2 x ULN) in the Enjaymo group and 35.77 µmol/l (1.75 x ULN) in the placebo group. The mean FACIT-Fatigue score was 31.67 and 32.99 in the Enjaymo and Placebo group respectively.

Efficacy was evaluated based on the proportion of patients who met the criteria of the primary endpoint: Increase in hemoglobin level from baseline of ≥ 1.5 g/dl at the time of treatment assessment (mean of weeks 23, 25 and 26), no blood transfusion from week 5 through week 26 and no treatment of cold agglutinin disease beyond the measures approved in accordance with the protocol from week 5 through week 26. A patient received a blood transfusion if the following haemoglobin thresholds were met: Haemoglobin levels < 7 g/dl or haemoglobin levels < 9 g/dl with symptoms. The prohibited therapies included rituximab alone or in combination with cytotoxic agents.
Secondary endpoints included the mean change from baseline in total bilirubin and the mean change from baseline in the FACIT-Fatigue score.
The efficacy results of Enjaymo in patients with cold agglutinin disease are described in Table 4.

Table 4 – Efficacy results in patients with cold agglutinin disease in the CADENZA study

| **Parameters** | **Statistic** | **Placebo N = 20** | **Enjaymo N = 22** | **Treatment effect** |
|---|---|---|---|---|
| **Responder** [a] | n (%)<br>(95% CI) | 3 (15.0)<br>(3.2; 37.9) | 16 (72.7)<br>(49.8; 89.3) | |
| | Odds ratio<br>(95% CI)<br>p-value: | | | 15.94<br>(2.88, 88.04)<br>< 0.001 |
| Patients with a mean increase in haemoglobin level from baseline of ≥ 1.5 g/dl | n (%) | 3 (15.0) | 16 (72.7) | NC |
| Patients not receiving blood transfusion from week 5 through week 26 (transfusion avoidance) | n (%) | 16 (80) | 18 (81.8) | NC |
| Patients receiving no protocol-prohibited cold agglutinin disease medications † during week 5 to week 26 | n (%) | 20 (100) | 19 (86.4) | NC |

[a] A responder was defined as a patient with an increase in hemoglobin level from baseline of ≥ 1.5 g/dl at the time of treatment assessment (mean value from weeks 23, 25 and 26), no blood transfusion from week 5 through week 26 and no treatment of cold agglutinin disease beyond the measures permitted per protocol from week 5 through week 26.
† Prohibited treatment included rituximab alone or in combination with cytostatics
NC not calculated

In Part A of the CADENZA study, the mean total bilirubin value at the time of treatment assessment was 12.12 µmol/l (mean change from baseline: - 22.13 µmol/l) in the Enjaymo group and 33.95 µmol/l (mean change from baseline: - 1.83 µmol/l) in the placebo group.

The mean FACIT-Fatigue score at the time of the treatment assessment was 43.15 in the sutimlimab group and 33.66 in the placebo group. For the Enjaymo group, a difference in mean change from baseline [LS (*least squares*) mean] of 8.93 (SE: 2.45, 95% CI: 4.0-13.85) compared to placebo was reported at the time of treatment assessment.

In Part B of the CADENZA study, the mean haemoglobin levels were maintained > 11 g/dl and sustained normalisation of the mean bilirubin levels was observed. Improvements on the FACIT-Fatigue scale observed in Part A were maintained.

After the last dose of Enjaymo in the study, signs and symptoms of recurrent hemolysis were observed. The mean hemoglobin value, nine weeks after the last dose in Part B, decreased by 2.41 g/dl (standard deviation (SD): 2.21) and the mean bilirubin value increased by 21.80 µmol/l (SD: 18.14) from the last available values on treatment.

Subgroup analysis
In terms of the primary endpoint, different response rates of Enjaymo compared to placebo were observed depending on gender:

Men (n=9): 60% (Enjaymo) versus 50% (placebo), women (n=33): 76.5% (Enjaymo) versus 6.3% (placebo)

*CARDINAL study*
Twenty-four (24) patients received 6,500 mg or 7,500 mg Enjaymo (depending on body weight) intravenously over approx. 60 minutes on day 0, day 7 and then every 14 days through week 25. After completion of the 6-month treatment period (Part A), 22 patients received Enjaymo for 24 months as part of an extension phase (Part B). The mean overall exposure to Enjaymo in Part A and B of the CARDINAL study was 132 weeks. The max. exposure to Enjaymo in the extension phase (B) was 151 weeks.
The mean age was 71.3 years (range: 55-85). The mean body weight was 67.8 kg (range: 40-112) and 62.5% of the study participants were female. At baseline, the mean haemoglobin level was 8.59 g/dl, the mean total bilirubin value was 53.26 µmol/l (2.6 x ULN) and the mean FACIT-Fatigue Score was 32.5. The mean number of transfusions within 6 months prior to enrolment was 3.2 (range: 1-19).

Efficacy was evaluated based on the proportion of patients who met the criteria for the primary endpoint: Increase in haemoglobin level from baseline of ≥ 2 g/dl or haemoglobin level of ≥ 12 g/dl at the time of treatment assessment (mean of weeks 23, 25 and 26), no blood transfusion from week 5 through week 26 and no treatment of cold agglutinin disease beyond the measures approved according to the protocol from week 5 through week 26.
Patients received a blood transfusion if the following haemoglobin thresholds were met: Haemoglobin levels < 7 g/dl or haemoglobin levels < 9 g/dl with symptoms. Prohibited treatment included rituximab alone or in combination with cytostatics.
The efficacy results of Enjaymo in patients with cold agglutinin disease are described in Table 5.

Table 5: Efficacy results in patients with cold agglutinin disease in the CARDINAL study – Part A

| **Parameter** | **Statistic** | **Enjaymo N = 24** |
|---|---|---|
| **Responders*** | n (%) | 13 (54) |
| Haemoglobin level ≥12 g/dL or<br>Increase in haemoglobin level from baseline of ≥2 g/dl | n (%) | 15 (63) |
| Haemoglobin level ≥12 g/dl | n (%) | 9 (38) |
| Increase in haemoglobin level from baseline of ≥2 g/dl | n (%) | 15 (63) |
| No blood transfusion from week 5 through week 26 (transfusion avoidance) | n (%) | 17 (71) |
| No treatment of cold agglutinin disease beyond the protocol-approved measures † from week 5 through week 26 | n (%) | 22 (92) |

[a] Responder was defined as a patient with an increase in haemoglobin level from baseline of ≥ 2 g/dl or haemoglobin level of ≥ 12 g/dl at the time of treatment assessment (mean of weeks 23, 25 and 26), no blood transfusion from week 5 through week 26 and no treatment of cold agglutinin disease beyond the measures approved according to the protocol from week 5 through week 26.
† Prohibited treatment included rituximab alone or in combination with cytostatics

In Part B of the CARDINAL study, mean haemoglobin levels were maintained at > 11 g/dl and sustained normalisation of mean bilirubin levels was observed.

After the last dose of Enjaymo in the study, signs and symptoms of recurrent hemolysis were observed. The mean hemoglobin value, nine weeks after the last dose in Part B, decreased by 2.28 g/dl (SD: 1.80) and the mean bilirubin value increased by 24.27 µmol/l (SD: 13.51) from on the last available data during treatment.

*Non-complement-mediated manifestations of cold agglutinin disease*

In addition to the symptoms mediated by hemolysis, patients with cold agglutinin disease may present cold-induced circulatory symptoms such as acrocyanosis and Raynaud’s phenomenon. No

improvement of cold-induced circulatory symptoms was observed with Enjaymo (see also the section “Warnings and precautions”).

*Paediatrics*

Sutimlimab has not been studied in patients under 18 years of age.

**Pharmacokinetics**

The pharmacokinetics of sutimlimab were investigated in 24 patients (CARDINAL) and 42 patients (CADENZA), including 51 patients who received 6,500 mg and 15 patients who received 7,500 mg as an intravenous infusion with an initial dose, followed by a loading dose 7 days later and then a maintenance dose every two weeks for 26 weeks. The total steady-state exposures for the recommended dosage regimens are listed in Table 6.

Table 6 – Mean (SD) steady-state exposure parameters of Enjaymo

| **CARDINAL and CADENZA** | **Dose (mg)** | **$C_{min}$ (µg/ml)*** | **$AUC_{SS}$ (µg·h/ml)*** |
|---|---|---|---|
| Mean value (SD) | 6,500 (n = 51)<br>7,500 (n = 15) | 1,397 (721)<br>1,107 (662) | 697,499 (256,232)<br>576,079 (253,816) |

* Abbreviations: $AUC_{ss}$= area under the curve between 2 consecutive doses after reaching steady state; $C_{min}$= trough concentration at steady state, defined as 1 hour before the next dose administration

After the start of treatment with sutimlimab, the steady state was reached by week 7, with an accumulation ratio of less than 2.

*Pharmacokinetic/pharmacodynamic relationships*

Sutimlimab concentrations above 100 µg/ml led to maximum inhibition of the classical complement pathway. The recommended dosage regimen showed sufficient exposure to sutimlimab at steady state to maximize the effects on haemoglobin, bilirubin and total C4 levels. The estimated minimum steady-state concentration for the half-maximum effect (EC50 or IC50) was similar for hemoglobin, C4 and bilirubin and ranged from 86 to 369 µg/ml.

*Absorption*

Sutimlimab is administered intravenously and is therefore completely bioavailable.

*Distribution*

The volume of distribution at steady state in central and peripheral compartments was approximately 5.8 l in patients with cold agglutinin disease.

*Metabolism*

Sutimlimab is a protein. It is generally known that antibodies are metabolised by degradation into small peptides and individual amino acids.

*Elimination*

The half-life of sutimlimab depends on the plasma concentration. Based on the total clearance (linear and non-linear clearance), the terminal elimination half-life of sutimlimab is 16 days.

*Linearity/non-linearity*

After administration of single doses, the clearance of sutimlimab at doses of less than 30 mg/kg (approx. 2 g) initially showed a strong decrease; the clearance becomes dose-independent between 60 and 100 mg sutimlimab per kg.

*Kinetics of special patient groups*

No clinically significant differences were observed in the pharmacokinetics of sutimlimab based on gender, age, ethnic origin, liver function disorder or renal function disorder. A population pharmacokinetic analysis showed that body weight and ethnic origin (Japanese and non-Japanese) affected the pharmacokinetics of sutimlimab. Lower exposure was observed in subjects with higher body weight. The effect of body weight on pharmacokinetics was taken into account by a body weight-dependent dosage recommendation. Even if a higher exposure (38% to 44%) was observed in Japanese subjects than in non-Japanese subjects, these differences did not have any clinical significance.

**Preclinical data**

*Repeated dose toxicity*

In repeat-dose toxicity studies with sutimlimab with exposures up to approx. 3-4 times the exposure at the recommended dose in humans, no effects on the reproductive organs of cynomolgus monkeys were observed.

*Genotoxicity and carcinogenicity*

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of sutimlimab.

*Reproductive toxicity*

A study on enhanced pre- and postnatal development (ePPND) in Javaner monkeys did not show any evidence of adverse developmental consequences with intravenous administration of sutimlimab between organogenesis and birth with exposures that correspond to approximately 2-3 times the AUC in humans at the recommended maximum dose.

**Other information**

*Incompatibilities*

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

*Shelf-life*

The medicinal product must only be used until the date stated on the package with “EXP”.

*Shelf life after preparation*

Chemical and physical stability after preparation of the Enjaymo solution for infusion was demonstrated for 16 hours at 18°C to 25°C or for 36 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately.
If not used immediately, the in-use storage duration and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2°C to 8°C or 8 hours at room temperature, taking into account the expected infusion duration at these storage times, unless vial opening and pooling into the infusion bag has taken place in controlled and validated aseptic conditions.

*Special precautions for storage*

Store in the refrigerator (2-8 °C). Do not freeze. Store the vial in the original packaging to protect the contents from light.
Do not shake. Keep out of the reach of children.

*Instructions for handling*

Enjaymo is provided as a solution in a single-dose vial and must be prepared aseptically by a healthcare professional as follows.

Preparation and administration of the undiluted solution:

1. Remove Enjaymo from the refrigerator. To prevent foaming, do not shake Enjaymo.
2. Inspect vials visually for particulate matter and discoloration prior to administration. The Enjaymo solution is an opalescent, colourless to slightly yellowish liquid. Do not administer if discolored or if other foreign particulate matter is present.
3. Withdraw the calculated volume of Enjaymo from the appropriate number of vials based on the recommended dosage (see Table 1 in section “Dosage/Administration“) and add to an empty infusion bag Discard the unused portion remaining in the vial.
4. For storage conditions, see the section “Shelf life after preparation”.
5. Prior to administration, allow the infusion solution to adjust to room temperature (18°C-25°C). Refer to Table 1 in section “Dosage/Administration“ for infusion rate. The infusion should be administered over a period of 1-2 hours. Administer Enjaymo infusion only through a 0.22 micron filter with a polyethersulfone (PES) membrane Infusion warmers may be used; do not exceed a temperature of 40 °C.

6. The infusion catheter and tubing should be primed with the dosing solution immediately before infusion and flushed immediately following completion of the infusion with a sufficient quantity (approximately 20 mL) of 0.9 % Sodium Chloride solution for injection.
7. No incompatibilities have been observed between Enjaymo infusion solution and infusion bags made of Di-(2-ethylhexyl)phthalate (DEHP) plasticized polyvinyl chloride (PVC), Ethyl Vinyl Acetate (EVA) and polyolefin (PO); administration sets made of DEHP-plasticized PVC, DEHP-free polypropylene (PP) and polyethylene (PE); and vial adapters made of polycarbonate (PC) and acrylonitrile-butadiene-styrene (ABS).

Preparation and administration of the diluted solution:

1. Remove Enjaymo from the refrigerator. To prevent foaming, do not shake Enjaymo.
2. Visually inspect vials for particulate matter and discoloration prior to administration. The Enjaymo solution is an opalescent, colourless to slightly yellowish liquid. Do not administer if discolored or if other foreign particulate matter is present.
3. Withdraw the calculated volume of Enjaymo from the appropriate number of vials based on the recommended dosage (see Table 2 in section “Dosage/Administration“) and add to an empty infusion bag. Dilute the calculated volume with 0.9 percent sodium chloride solution for injection to a total volume of 500 ml. Discard the unused portion remaining in the vial.
4. For storage conditions, see the section “Shelf life after preparation”.
5. Prior to the administration, allow the solution for infusion to adjust to room temperature (18°C-25°C). For the infusion rate, refer to Table 2 in section “Posology and method of administration”. The infusion should be administered over a period of 1-2 hours. Administer Enjaymo infusion only through a 0.22 micron filter with a polyethersulfone (PES) membrane Infusion warmers may be used; do not exceed a temperature of 40 °C.
6. The infusion catheter and tubing should be primed with the dosing solution immediately before infusion and flushed immediately following completion of the infusion with a sufficient quantity (approximately 20 mL) of 0.9 % Sodium Chloride solution for injection.
7. No incompatibilities have been observed between Enjaymo infusion solution and infusion bags made of Di-(2-ethylhexyl)phthalate (DEHP) plasticized polyvinyl chloride (PVC), Ethyl Vinyl Acetate (EVA) and polyolefin (PO); administration sets made of DEHP-plasticized PVC, DEHP-free polypropylene (PP) and polyethylene (PE); and vial adapters made of polycarbonate (PC) and acrylonitrile-butadiene-styrene (ABS).

*Special precautions for disposal*

Any unused medicinal product or waste material must be disposed of in accordance with national requirements.

**Authorisation number**

68074

**Packs**

Enjaymo 1,100 mg/22 ml solution for infusion, pack of 1 vial [A]
Enjaymo 1,100 mg/22 ml solution for infusion, pack of 6 vials [A]

**Marketing authorisation holder**

sanofi-aventis (suisse) sa, 1214 Vernier

**Date of revision of the text**

October 2022