Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Sutimlimab (cold agglutinin disease)

of 15 June 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient sutimlimab on 1 January 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 19 December 2022.

Sutimlimab for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 3 April 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G23-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of sutimlimab.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Sutimlimab (Enjaymo) in accordance with the product information

Enjaymo is indicated for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD).

Therapeutic indication of the resolution (resolution of 15 June 2023):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of sutimlimab is assessed as follows:

Hint for a minor additional benefit.

Justification:

The pharmaceutical company submitted data from the two pivotal, phase III CADENZA and CARDINAL studies for the benefit assessment. Both studies have been completed.

CADENZA

The CADENZA study is a multicentre, randomised, double-blind, placebo-controlled study.

Adult patients with a confirmed diagnosis of primary CAD and an Hb ≤ 10.0 g/dl who had one or more of the following CAD-related signs or symptoms for three months prior to baseline were enrolled: Symptomatic anaemia (defined by: fatigue, feeling of weakness, shortness of breath, palpitation, rapid heartbeat, drowsiness, chest pain), acrocyanosis, Raynaud's syndrome, haemoglobinuria, debilitating circulatory symptoms, serious vascular event (including thrombosis). Vaccinations against encapsulated bacterial pathogens (Neisseria meningitis, Meningococcus serotype B, Haemophilus influenzae and Streptococcus pneumoniae) within five years prior to enrolment were required for participation in the study. Patients who had received a blood transfusion within six months prior to screening or more than one blood transfusion within 12 months prior to screening were excluded from participation in the study.

The CADENZA study was divided into two parts (A and B). For part A of the study, patients were randomised in a 1:1 ratio to either the intervention arm (sutimlimab; N = 22) or the control arm (placebo; N = 20) in an unstratified manner. After completion of a 26-week randomised controlled phase, a transition to an open-label extension phase was possible in part B, where participants could switch from the control arm to the treatment arm and be treated with sutimlimab for 12 months.

The primary endpoint of the study was the response to therapy, additional endpoints were collected on symptomatology, health-related quality of life and adverse events.

CARDINAL

The CARDINAL study is a multicentre, single-arm study.

Adult patients with a confirmed diagnosis of primary CAD and an Hb ≤ 10.0 g/dl who had one or more of the following CAD-related signs or symptoms for three months prior to baseline were enrolled: Symptomatic anaemia (defined by: fatigue, weakness, shortness of breath, palpitation, rapid heartbeat, drowsiness, chest pain), acrocyanosis, Raynaud's syndrome, haemoglobinuria, debilitating circulatory symptoms, serious vascular event (including thrombosis). At least one documented blood transfusion within six months prior to enrolment in the study was also required for study participation. Vaccinations against encapsulated bacterial pathogens (Neisseria meningitis, Meningococcus serotype B, Haemophilus influenzae and Streptococcus pneumoniae) within five years prior to participation in the study were also inclusion criteria.

The CARDINAL study was also divided into two parts (A and B). Part A of the study consisted of a 26-week treatment phase followed by part B with a two-year follow-up treatment phase.

The primary endpoint of the study (part A) was the response to therapy, additional endpoints were collected on symptomatology, health-related quality of life and adverse events.

Assessment basis

The randomised controlled part of the CADENZA study (part A) is used for the assessment of the extent of the additional benefit of sutimlimab, as these are controlled data that allow comparative statements and are to be assigned to a higher degree of evidence than the uncontrolled data of the CARDINAL study. However, the CARDINAL study is presented additionally especially due to the fact that the CARDINAL study investigated a different population with regard to patients with a blood transfusion in their recent medical history than the CADENZA study.

Mortality

Overall survival was not collected as a separate endpoint in the CADENZA study. Fatalities were recorded as part of the assessment of the adverse events. Not a single death occurred in any study arm within part A. From the available data, there is therefore no relevant difference between the treatment arms.

Morbidity

Health status

In the CADENZA study, patient-reported health status was assessed using the EQ-5D-5L visual analogue scale.

There is no statistically significant difference between the treatment arms.

Fatigue

Data on fatigue were collected in the CADENZA study using the FACIT Fatigue questionnaire.

There is a statistically significant difference in the mean change from baseline to treatment assessment timepoint (TAT; weeks 23, 25 and 26) to the advantage of sutimlimab. The percentage of missing values on the TAT is 14% in the sutimlimab arm and 0% in the comparator arm. Based on the standardised mean difference (Hedges' g), a clinically relevant difference is assumed.

Thromboembolic events

In the CADENZA study, one thromboembolic event occurred in the intervention arm; none in the control arm. From the available data, there is therefore no relevant difference between the treatment arms.

Quality of life

Data on health-related quality of life were collected in the CADENZA study using the Short-Form 12 Health Survey (SF-12).

In the process, a statistically significant difference between the treatment arms was observed neither for the mental component summary (MCS) score nor the physical component summary (PCS) score.

Side effects

Adverse events (AEs) in total

Nearly all patients of the intervention and control arm experienced an adverse event. The results were only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs.

AEs of special interest

In detail, there are no statistically significant or relevant differences between the treatment arms, even for the AEs of special interest for which the pharmaceutical company submitted p values.

When interpreting the results on side effects, it should be conditionally noted that the pharmaceutical company submitted p values for the endpoints on side effects for the CADENZA study only for the overall rates and for a part of the AEs of special interest. Effect estimators and associated confidence intervals were not reported by the pharmaceutical company.

Overall assessment

Results of the CADENZA and CARDINAL studies are available for the benefit assessment of sutimlimab for the treatment of haemolytic anaemia in adults with cold agglutinin disease (CAD). The present assessment is based on the randomised controlled part A of the CADENZA study, in which sutimlimab was compared with placebo.

With regard to overall survival, no deaths occurred in either study arm. From the available data, there is therefore no relevant difference.

In the endpoint category of morbidity, results are available on health status, fatigue and thromboembolic events. Thereby, a statistically significant and clinically relevant difference to the advantage of sutimlimab is shown for the endpoint of fatigue. Given that fatigue is one of the main symptoms of cold agglutinin disease, this effect is considered to be a significant advantage for patients.

With regard to health-related quality of life, no statistically significant differences were observed between the treatment arms, based on the SF-12 results.

Also with regard to side effects, there were also no assessment-relevant differences between sutimlimab and placebo overall.

In the overall analysis of the present results, the advantage in the endpoint of fatigue is not offset by a disadvantage. As a result, the G-BA classified the extent of the additional benefit of sutimlimab for the treatment of haemolytic anaemia in adults with cold agglutinin disease (CAD) as low.

Significance of the evidence

The present assessment is based on the randomised, controlled part A of the CADENZA study.

Limitations with regard to the risk of bias at study level result from the fact that in the CADENZA study treatment decisions (e.g. on red blood cell concentrates) were made, among other things, on the basis of the Hb values. Unblinding of the treating study personnel by knowledge of the Hb values that were increased under sutimlimab can therefore not be ruled out.

At the endpoint level, the results for the patient-reported endpoints, especially those for the endpoint of fatigue, are considered to be prone to a high risk of bias due to high percentages of missing values in the evaluation, which are differentially large between the study arms.

Limitations also result from the fact that the pharmaceutical company does not provide effect estimators including confidence intervals for the endpoints on side effects, but only reports selected p values.

In the overall assessment, this results in the classification of significance of the evidence in the "hint" category

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Enjaymo with the active ingredient sutimlimab. Enjaymo was approved as an orphan drug in the following therapeutic indication:

"Enjaymo is indicated for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD)."

The pharmaceutical company submitted data from the pivotal phase III CADENZA and CARDINAL studies for the benefit assessment. The randomised controlled part of the CADENZA study is used to assess the extent of the additional benefit. The single-arm CARDINAL study is presented additionally.

With regard to overall survival, no deaths occurred in either of the CADENZA study arms. From the available data, there is therefore no relevant difference.

In the endpoint category of morbidity, results are available on health status, fatigue and thromboembolic events. Thereby, a statistically significant and clinically relevant difference to the advantage of sutimlimab is shown for the endpoint of fatigue.

With regard to health-related quality of life, no statistically significant differences were observed between the treatment arms, based on the SF-12 results.

Also with regard to side effects, there were also no assessment-relevant differences between sutimlimab and placebo overall.

In the overall assessment, the G-BA classifies the extent of the additional benefit of sutimlimab based on the benefit for the endpoint of fatigue as low.

The significance of the evidence is classified in the "hint" category.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The procedure of the pharmaceutical company is mathematically comprehensible. It is assumed that the data is in a largely plausible order of magnitude.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Enjaymo (active ingredient: sutimlimab) at the following publicly accessible link (last access: 2 May 2023):

https://www.ema.europa.eu/en/documents/product-information/enjaymo-epar-product-information_en.pdf

Treatment with sutimlimab should only be initiated and monitored by specialists who are experienced in the treatment of patients with haematological diseases.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. In particular, the training material contains information and warnings on the risk of serious infections and meningococcal infections.

Patients shall be vaccinated according to the current recommendations for patients with persistent complement deficiency diseases, including vaccines against meningococci and streptococci. Patients should receive booster vaccinations according to local recommendations.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 May 2023).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Sutimlimab	Continuously, every 14 days	26.1	1	26.1

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg).[2]

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Sutimlimab	7500 mg	7500 mg	7 x 1100 mg	26.1	182.7 x 1100 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Sutimlimab	6 INF	€ 8,541.30	€ 2.00	€ 835.20	€ 7,704.10
Abbreviations: INF = infusion solution					

LAUER-TAXE® last revised: 15 May 2023

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Sutimlimab

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 19 December 2022, the pharmaceutical company submitted a dossier for the benefit assessment of sutimlimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 3 April 2023 together with the IQWiG

assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 24 April 2023.

The oral hearing was held on 2 May 2023.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 25 May 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 June 2023, and the proposed resolution was approved.

At its session on 15 June 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 March 2023	Information of the benefit assessment of the G-BA
Subcommittee Medicinal products	2 May 2023	Conduct of the oral hearing
Working group Section 35a	9 May 2023 30 May 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	6 June 2023	Concluding discussion of the draft resolution
Plenum	15 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 June 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken