Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V
Crizanlizumab (Prevention of vaso-occlusive crises in sickle cell disease)

of 20 May 2021

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 a rare disease (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 of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. 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 evaluation 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 Ordinance on the Benefit Assessment of Pharmaceuticals (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 €50 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, subsection 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 authorisation 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 legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). 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 first submission on the market of the combination of active ingredient crizanlizumab in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 December 2020. 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, number 1 VerfO on 26 November 2020.

Crizanlizumab indicated for the prevention of vaso-occlusive crises in sickle cell disease is approved as a medicinal product for the treatment of a rare disease 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 of the sentence German Social Code, Book Five (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 authorisation 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 01 March 2021 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-28) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation 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 crizanlizumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of crizanlizumab (Adakveo) in accordance with the product information

Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution from the 20/05/2021):

- see therapeutic indication according to marketing authorisation

2.1.2 Extent of the additional benefit and the significance of the evidence

In summary, the added benefit of crizanlizumab (with or without hydroxyurea) is assessed as follows:

Hint for a minor additional benefit.

Justification:

The pharmaceutical company has submitted data from the pivotal, randomised, double-blind, placebo-controlled Phase II SUSTAIN study for benefit assessment. This three-arm study compared treatment with crizanlizumab at two different doses (2.5 mg/kg and 5.0 mg/kg) versus treatment with placebo. Concomitant treatment with hydroxyurea (HU) was allowed in all three study arms. The proportion of patients with concomitant HU treatment was limited to 65%.

In the study, crizanlizumab was examined in the form of the investigational product “SelG1”, while the market product contains the active ingredient in the version “SEG101” following an adjustment of the manufacturing process that has since taken place. “SelG1” and “SEG101” are considered by the EMA to be equivalent in terms of pharmacokinetics and pharmacodynamics.

Patients between 16 and 65 years of age with sickle cell disease should be included and should have between 2 and 10 vaso-occlusive pain crises (VOCs) in the 12 months prior to time of enrolment. Randomisation was 1:1:1 after concomitant treatment with HU (yes/no) and the number of VOCs during the past 12 months (2-4 or 5-10 VOCs). The present benefit assessment is based on the comparison of the study arm with the 5 mg/kg crizanlizumab dose in compliant with marketing authorisation (intervention arm) and the placebo study arm (comparator arm).

In terms of genotypes, approximately 70%-72% of patients in the intervention and comparison arms had an HbSS genotype, and approximately 12%-13% of patients had an HbSC genotype. In addition, approximately 5% and 10% of patients in the intervention arm had an HbSβ0-thalassemia and HbSβ+-thalassemia genotype, respectively. In the comparator arm, the corresponding percentages are about 11% and 2%, respectively.

The study was divided into three phases (screening, treatment and follow-up). The treatment phase consisted of 50 weeks of treatments and a treatment completion visit at week 52. The follow-up visit should take place approximately 8 weeks after the last dose (usually week 58).

Treatment was provided until the occurrence of AE leading to discontinuation, unacceptable QTc interval elevations leading to discontinuation, pregnancy, withdrawal of informed consent, death, otherwise justified study discontinuation, or completion of 50 weeks of treatment. In the SUSTAIN study, 24 patients in each of the intervention and comparison arms discontinued treatment prematurely, representing 36% and 37% of patients in these arms, respectively.

The primary endpoint of the study was the annual rate of VOCs; additional endpoints were collected on symptomatology, health-related quality of life, and adverse events.

The SUSTAIN study, which was conducted at a total of 60 study sites in the United States, Brazil and Jamaica, ended in 2016.

<u>Mortality</u>

Overall survival was not collected as a separate endpoint in the SUSTAIN study. Deaths were recorded as part of the adverse event assessment, and two deaths were descriptively reported in each of the two study arms.

From the available data, there is no relevant difference between the treatment arms.

Morbidity

Vaso-occlusive crises (VOC)

Sickle cell disease-associated vaso-occlusive pain crises and other vaso-occlusive complications felt by patients are considered patient-relevant events.

In the SUSTAIN study, the event of a vaso-occlusive pain crisis was defined as:

(a) an acute episode of pain,
(b) without a cause of pain other than a vaso-occlusive event,
(c) where the presence in a medical establishment and
(d) oral or parenteral treatment with opioids or parenteral treatment with non-steroidal anti-inflammatory drugs (NSAIDs) were necessary.

All four criteria had to apply. The following events associated with vaso-occlusive crises were also considered vaso-occlusive pain crises in the SUSTAIN study: acute chest syndrome (ATS), liver sequestration, splenic sequestration, and priapism. The latter also with the need for presentation to a medical establishment. The events ATS, liver sequestration, splenic sequestration, priapism and “uncomplicated VOC”, i.e. vaso-occlusive pain crises in the narrower sense, which were defined solely by criteria a) to d), were also collected as separate subclassifications.

In the SUSTAIN study, VOCs were to be recorded throughout the treatment phase (including a treatment completion visit) until the follow-up visit. After any treatment discontinuation, the treatment completion visit should be conducted as soon as possible. In addition, the follow-up visit should occur approximately 8 weeks after the last dose, if possible. All events classified as VOC by the respective investigator had to be adjudicated additionally by a Crisis Review Committee (CRC).

Endpoints on VOC - annual rate VOC

Annual rate VOC was the primary endpoint of the SUSTAIN study. To evaluate the endpoint, VOCs occurring during the treatment phase in study participants were mathematically annualised based on the ITT population.

The primary analysis of the endpoint mainly included pain crises in the narrower sense (“uncomplicated VOC”) with 109 versus 166 events (intervention vs comparison arm) and 12 ATS events each.

In addition to the primary analysis for the endpoint Annual rate of VOC, sensitivity analyses were partly pre-specified, partly performed and reported at the request of the EMA. This was done in particular against the background of the uncertainties described in the EPAR regarding the appropriateness of the statistical model used for the primary analysis, the adjudication process of the CRC on VOC, and the high rate of study participants who discontinued the study prematurely. The sensitivity analyses are based on a negative binomial regression model, which was considered more appropriate by the EMA and is also considered more appropriate in the context of the present benefit assessment, as there are uncertainties about the extent to which the statistical assumptions required for the Wilxocon rank sum test used in the primary analysis are fulfilled.

Accordingly, major differences within the sensitivity analyses exist in the data basis (CRC vs investigator) as well as the application of imputation methods to replace missing values of study participants who discontinued therapy before the end of the study.

As a result, the pre-specified sensitivity analysis PS-1 (according to CRC), in which no imputation of missing values was performed, shows a statistically significant advantage of crizanlizumab (+ HU, if applicable) over placebo (+ HU, if applicable), while the two post-hoc sensitivity analyses with imputation PhS-M6a (according to CRC) and PhS-M6b (according to investigator) no longer show statistically significant differences.

Endpoints to VOC - Time to first VOC

The endpoint time to first VOC was defined as the number of months from randomisation to the date of first VOC. For the endpoint (according to CRC), there is a statistically significant advantage of crizanlizumab (+ HU, if applicable) over placebo (+ HU, if applicable). In the intervention arm, the time to first VOC was prolonged by a median of approximately 2.7 months.

Conclusion on VOC

Overall, the available data on VOCs are subject to uncertainties. These mainly consist of the high rate of study participants who discontinued treatment prematurely. Since in the SUSTAIN study there was no follow-up of VOC at treatment discontinuation until the end of the study, the sensitivity analyses cannot compensate in toto for the bias resulting from the high rate of study discontinuations, especially for the endpoint of annual rate VOC, but can only represent an approximation of the actual treatment effect of crizanlizumab. Furthermore, with regard to the data basis (CRC vs investigator), potentially informative information on the CRC's approach to adjudicating VOCs is not available, and it remains to be noted that a total of five study participants, three in the intervention arm and two in the comparison arm, did not meet the inclusion criterion of two to ten VOCs in the 12 months prior to study inclusion, but only one of these participants in the intervention arm was addressed in the PhS-M6b sensitivity analysis. With regard to the time-to-event analysis, the interpretation of the results is also limited by the fact that in the SUSTAIN study the time of onset of a VOC was not defined and thus not standardised. It should also be noted that the SUSTAIN study does not provide any data on the end-organ damage resulting from VOCs in the long term, which is considered to be of high importance in the present therapeutic indication, in accordance with the comments of clinical experts in the written statement procedure.

However, in the overall consideration of the results of both endpoints on VOCs, it is assumed, despite remaining uncertainties, that there is an effect towards a reduction or a delay in the occurrence of VOCs. This is due to the fact that in particular the effect estimators of the sensitivity analyses for the endpoint Annual rate VOC consistently point towards the efficacy of crizanlizumab (+ HU, if applicable), and statistical significance is given for the result for the endpoint Time to first VOC. Thus, an advantage of crizanlizumab (+ HU, if applicable) over placebo (+ HU, if applicable) is observed in this regard.

Pain (BPI-LF)

In the SUSTAIN study, patients' perceived pain was assessed using the Brief Pain Inventory - long form (BPI-LF). In this regard, evaluations are available for the two scales "pain intensity" and "impairment due to pain" as well as a post hoc evaluation for the item "strongest pain".

However, the return rates on BPI-LF were already below 70 % in the intervention arm at the first measurement point and also in the further course of the study, so that the significance of the results cannot be regarded as reliable. The results on BPI-LF are therefore not used to assess the extent of additional benefit.

In the overall analysis of the results for the category Morbidity, conclusions on the extent of additional benefit can only be derived from the endpoints on VOC. Despite remaining uncertainties, an effect towards a reduction or a delay of the occurrence of VOC to the

advantage of crizanlizumab (+ HU, if applicable) compared to placebo (+ HU, if applicable) is shown. On the basis of the available data, the magnitude of the effect is assessed as a relevant improvement, but no more than a minor improvement.

Quality of life

Short Form Health Survey (SF-36)

Data on health-related quality of life were collected in the SUSTAIN study using the SF-36, with the mental component score (MCS) and physical component score (PCS) considered separately.

Responder analyses were not reported for either score, so mean difference analyses (MMRM) are used. Limitations result from the fact that the results are only sufficiently reliable for the period from the start of treatment to week 26, since at later points in time the return rates are already below 70 %. As a result, there is no statistically significant difference between the treatment groups at week 26 in either score.

Side effects

Adverse events (AE) in total

AEs occurred in approximately 90% of patients in both the intervention and comparison arms. The results were only presented as a supplement.

severe AE

In the SUSTAIN study, AEs were classified according to severity as mild (no impairment of daily activities), moderate (impairment of daily activities) and severe (prevention of daily activities). The classification of the AEs according to severity performed by the pharmaceutical company was thus neither performed according to CTCAE nor according to any other established or validated indication-specific classification. Therefore, the available data on the endpoint Severe AE are considered not assessable.

severe AEs (SAE), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints SAEs and Treatment discontinuation due to AEs.

In the overall assessment of the endpoint category Side effects, there are neither advantages nor disadvantages of crizanlizumab (+ HU, if applicable) compared to placebo (+ HU, if applicable).

Overall assessment

For the benefit assessment of crizanlizumab as monotherapy or adjunctive therapy to hydroxyurea (HU) for the prevention of recurrent vaso-occlusive crises (VOCs) in patients with sickle cell disease aged 16 years and older, the results of the SUSTAIN study are available. The study, completed in 2016, compared crizanlizumab (+ HU, if applicable) versus placebo (+ HU, if applicable).

For overall survival, two deaths were descriptively reported in each study arm, which were documented during the AE survey. Effect estimates are not available, so that the available data do not allow a statement on the extent of the additional benefit.

For the endpoint category Morbidity, results on the occurrence of VOCs are available from the endpoints Annual rate VOC and Time to first VOC. For the endpoint annual Rate of VOCs, the sensitivity analyses used for the evaluation show results that are partly significant and partly non-significant. The endpoint Time to first VOC shows a statistically significant benefit of crizanlizumab (+ HU, if applicable). In the overall assessment of both endpoints, despite

remaining uncertainties, it is assumed that there is an effect of crizanlizumab (+ HU, if applicable) compared to placebo (+ HU, if applicable) towards a reduction or a delay in the occurrence of VOC. On the basis of the available data, the magnitude of the effect is assessed as a relevant improvement, but no more than a minor improvement.

With regard to patient-reported quality of life, the results of the SF-36 showed no statistically significant difference between the treatment groups.

With regard to side effects, overall neither advantages nor disadvantages of crizanlizumab (if applicable in combination with HU) compared to placebo (if applicable in combination with HU) can be derived. However, the data on the endpoint Severe AEs are not considered assessable, as the classification by severity was neither based on the CTCAE nor on another established or validated indication-specific classification.

In the overall assessment, based on the positive effect of a reduction or a delay in the occurrence of VOCs, the G-BA classifies the extent of the additional benefit of crizanlizumab (+ HU, if applicable) compared to placebo (+ HU, if applicable) as low for the prevention of recurrent vaso-occlusive crises (VOCs) in patients with sickle cell disease aged 16 years and older.

Significance of the evidence

The present assessment is based on the results of the double-blind, placebo-controlled Phase II SUSTAIN study.

The risk of bias at the study level is considered high. Limitations across endpoints with regard to the significance of the evidence result in particular from the high number of patients with premature study discontinuation. In both study arms, 24 patients each discontinued the study prematurely, representing 36% and 37% of patients in the intervention and comparison arms, respectively.

With regard to the endpoints on VOC, there are uncertainties about the extent to which the operationalisation of VOC carried out in the SUSTAIN study can be directly transferred to the German health care context. Vaso-occlusive pain crises in the narrower sense (“uncomplicated VOC”), which represented the majority of events according to the available data, were linked to the prerequisites of presentation in a medical facility and oral or parenteral treatment with opioids or parenteral treatment with NSAIDs for assessment. These events may thus be strongly dependent on the respective context of care, and in this respect it should be taken into account that all participating study centres were located outside Germany or Europe. Consequently, it also remains uncertain whether the SUSTAIN study ensured complete coverage of vaso-occlusive crises, as events treated outside medical facilities, such as VOCs self-treated by patients, were not included.

In addition, the data situation on VOC per se is also subject to uncertainties, which result in particular from the high rate of patients with premature study discontinuation and the lack of follow-up of VOC until the end of the study in these cases.

Overall, this results in the classification of the significance of the evidence in the category “hint”.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of crizanlizumab finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

The data on VOC available for the present assessment from the phase II SUSTAIN study are subject to uncertainties, in particular due to the high number of patients with premature study discontinuation. Against the background that the drug Adakveo with the active ingredient crizanlizumab was approved under “special conditions”, results from the currently ongoing

Phase III STAND study are to be reported to the EMA in this regard. According to the EPAR, the primary analysis of the results of the STAND study is to be submitted to the EMA by December 2025.[2]

Since more clinical data are expected which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of crizanlizumab. The time limit enables the inclusion of the expected results from the phase III study STAND in the benefit assessment of the drug according to Section 35a SGB V. For this purpose, a time limit of the resolution until 1 December 2025 is considered appropriate.

Conditions for the limitation:

For the new benefit assessment after expiry of the deadline, the results on all patient-relevant outcomes used for the proof of an additional benefit, including the results of the STAND study, are to be presented in the dossier.

A change in the time limit can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 1 number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of crizanlizumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of crizanlizumab (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO).

The possibility that a benefit assessment for crizanlizumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2 VerfO and Chapter 5, Section 12, No. 2 VerfO) remains unaffected hereof.

2.1.4 Summary of the assessment

The present assessment concerts the benefit assessment of the new medicinal product Adakveo with active ingredient crizanlizumab. Adakveo has been approved under special conditions as an orphan drug in the following indication:

“Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.“

The pharmaceutical company has submitted data from the pivotal, randomised, double-blind, placebo-controlled Phase II SUSTAIN study for benefit assessment.

For overall survival, two deaths were descriptively reported in each study arm.

In the overall analysis of the results for the category Morbidity, conclusions on the extent of additional benefit can only be derived from the endpoints on VOC. In the overall assessment of the endpoints Annual rate of VOC and Time to first VOC, it is assumed, despite remaining uncertainties, that there is an effect of crizanlizumab (+ HU, if applicable) compared to placebo (+ HU, if applicable) towards a reduction or a delay in the occurrence of VOC. On the basis of the available data, the magnitude of the effect is assessed as a relevant improvement, but no more than a minor improvement.

In the category Quality of life, the results on the SF-36 show no statistically significant difference between the treatment groups.

[2] CHMP assessment report Adakveo; European Medicines Agency; 23 July 2020

With regard to side effects, overall neither advantages nor disadvantages of crizanlizumab (if applicable in combination with HU) compared to placebo (if applicable in combination with HU) can be derived.

In the overall assessment, based on the positive effect of a reduction or a delay in the occurrence of VOCs, the G-BA classifies the extent of the additional benefit of crizanlizumab (+ HU, if applicable) compared to placebo (+ HU, if applicable) as low for the prevention of recurrent vaso-occlusive crises (VOCs) in patients with sickle cell disease aged 16 years and older.

In particular, due to the high number of patients with premature study discontinuation and uncertainties regarding the statistical analyses of the results on VOC as well as the transferability of the operationalisation of VOC to the German health care context, the result is a hint for an additional benefit based on the significance of the evidence.

The validity of the resolution is limited to 01 December 2025.

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, but is subject to uncertainties in the individual calculation steps. In this context, the calculation step for determining the proportion of patients with VOCs requiring treatment tends to lead to an underestimation, since the routine data analysis used for this purpose only assesses those VOCs that were treated in the context of an emergency, on an outpatient or inpatient basis, and thus VOCs that do not result in direct physician contact are not taken into account.

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 Adakveo (active ingredient: crizanlizumab) at the following publicly accessible link (last access: 08 April 2021):

https://www.ema.europa.eu/en/documents/product-information/adakveo-epar-product-information_de.pdf

Treatment with crizanlizumab should be initiated and monitored by doctors experienced in treating patients with sickle cell disease.

This medicinal product has been authorised under a so-called “conditional approval” scheme. The EMA will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

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: 01 May 2021).

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 is patient-individual 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.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg for adults aged 18 and over and 65.2kg for adolescents aged 16 and over).[3]

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose strengths as well as the scalability of the respective dosage form.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Crizanlizumab	Once every 28 days	13,0	1	13,0
plus				
Hydroxycarbamide	1 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Crizanlizumab	5 mg/kg = 326 mg - 385 mg	326 mg - 385 mg	4 x 100 mg	13,0	52 x 100 mg
plus					

3 Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Hydroxycarbamide	15 mg/kg = 978 mg - 30 mg/kg = 2,310 mg	978 mg - 2,310 mg	1 x 1,000 mg - 2 x 1,000 mg + 3 x 100 mg	365	365 x 1,000 mg - 730 x 1,000 mg + 1,095 x 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

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					
Crizanlizumab	1 IFC	€ 1,906.73	€ 1.77	€ 105.62	€ 1,799.34
Hydroxycarbamide 1,000 mg	30 FCT	€ 959.28	€ 1.77	€ 52.50	€ 905.01
Hydroxycarbamide 100 mg	60 FCT	€ 200.71	€ 1.77	€ 10.50	€ 188.44
Abbreviations: IFC = concentrate for the preparation of an infusion solution; FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 May 2021

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 or patient information leaflet, the differences 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.

For the cost representation no additionally required SHI services are considered.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

3. Bureaucratic costs

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 26 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of crizanlizumab to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 01 March 2021 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 the written statements was 22 March 2021.

The oral hearing was held on 06 April 2021.

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 were discussed at the session of the subcommittee on 11 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 February 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	30 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	6 April 2021	Conduct of the oral hearing
Working group Section 35a	13 April 2021 20 April 2021 4 May 2021	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	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken