Justification

Gemeinsamer Bundesausschuss

to 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 Caplacizumab (New Therapeutic Indication: Acquired Thrombotic Thrombocytopenic Purpura, 12 to < 18 Years)

of 7 January 2021

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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 of the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not 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, Nos. 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 € 50 million during the last 12 calendar months. In accordance with 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 in accordance with 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 compared 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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 provided is assessed exclusively on the basis of the pivotal 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 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 of 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient caplacizumab in accordance with Chapter 5, Section 8, number 2 of the Rules of Procedure of the G-BA (VerfO) is 15 July 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 2 VerfO on 3 July 2020.

Caplacizumab for the treatment of adolescents from 12 years weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasmapheresis and immunosuppression is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half 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 by the G-BA on the basis of the pivotal studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess 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 15 October 2020 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 assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-13) prepared by the IQWiG, and the written statements submitted in the written and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of caplacizumab.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of caplacizumab (Cablivi) in accordance with the product information

Cablivi is indicated for the treatment of adults and adolescents of 12 years of age and older weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

Therapeutic indication of the resolution (resolution of 7 January 2021):

Cablivi is indicated for the treatment of adolescents of 12 years of age and older weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

2.1.2 Extent of the additional benefit and significance of the evidence

Adolescents from 12 to < 18 years weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP)

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

Hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Justification:

For adolescents from 12 to < 18 years weighing at least 40 kg experiencing an episode of aTTP, there are no clinical studies in which caplacizumab has been used and investigated. The pharmaceutical company cites two individual case reports for the designated patient population of adolescents. The individual case reports are not used for the benefit assessment because it is not possible to estimate the reliability of data and the extent of the additional benefit based on individual case reports.

For the benefit assessment of caplacizumab for adolescents from 12 to < 18 years weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), the pharmaceutical company refers to the HERCULES study, among others, in the context of an evidence transfer from adults to adolescents with aTTP. The HERCULES study is a completed, multi-centre, double-blind, placebo-controlled, Phase III study with a parallel-group design that evaluated the efficacy and safety of caplacizumab when administered as part of combination therapy (daily plasma exchange and immunosuppressive therapy) in adult aTTP patients. Based on the HERCULES study, the benefit assessment of caplacizumab in adults with aTTP has already been conducted. By resolution of 22 March 2019, a hint for a non-quantifiable additional benefit was identified in this procedure for caplacizumab in combination with plasmapheresis and immunosuppression compared with plasmapheresis and immunosuppression. [2]

To demonstrate the comparability of the pharmacokinetics and mechanism of action of caplacizumab in adult and adolescent patients, the pharmaceutical company draws on the results of the pharmacokinetic (PK)/pharmacodynamic (PD) modelling/simulation study ALX0681-MS-01, which is the basis of the current marketing authorization extension. This consists of two parts: a PK/PD modelling study with two PK/PD models in adults and the simulations based on them in children and adolescents from 2 to 18 years of age (ALX0681-MS-01-SIM). Based on the final PK/PD model, ALX0681-MS-01-SIM simulates the active ingredient concentration and pharmacokinetic response in adolescent and paediatric patients with aTTP after treatment with caplacizumab. Simulations were also performed with an additional differentiation between 2 weight divisions (< 40 kg and ≥ 40 kg).

The assessment report from the European Medicines Agency (EMA)[3] states that the adult PK/PD population modelling study as well as the paediatric patient simulations based on it are part of a paediatric investigation plan for caplacizumab agreed with the EMA. The EMA used the PK/PD modelling as well as simulation studies as the sole reference for the extension of approval for caplacizumab in the designated therapeutic indication. However, it is noted that no clinical data in the paediatric population have been presented to support the simulation results.

Overall, the EMA assesses the results of the pharmacokinetics simulation study as sufficiently robust to support the posology of caplacizumab in paediatric patients weighing more than 40 kg and agrees to an extension of approval for adolescents 12 to < 18 years of age and weighing at least 40 kg. Additional clinical data are not considered necessary to include adolescents in

[2] Caplacizumab for adult patients with aTTP – Resolution of 22 March 2019
[3] Variation Assessment Report; EMEA/H/C/004426/II/0021; Cablivi; 30 April 2020

the therapeutic indication. Based on the mechanism of action of caplacizumab, the comparable pathogenesis of aTTP in children and adults, and the evidence to date on treatment effects in children, the EMA believes that caplacizumab is likely to have comparable efficacy and safety in children as it does in adults.

For the G-BA, these findings of the EMA form the minimum requirements for a transfer of evidence, which is the basis of the present benefit assessment.

In the present benefit assessment, the transfer of evidence is not followed in this case because of the following points:

Comparability of the disease and prognosis

For comparability of the disease and prognosis of adults and adolescents aged 12 years and older, the pharmaceutical company refers in the dossier to retrospective evaluations and derives from these the comparability of the pathophysiology and clinical picture of the disease aTTP between adults and adolescents.

The retrospective evaluations were selected by the pharmaceutical company only on the basis of an orienting search and not systematically. The evaluations are also subject to a high risk of bias because of the low number of paediatric or adolescent patients included, the non-systematic selection of patients, and therefore questionable representativeness or unclear selection criteria. Also, no relevant age-specific statements regarding the disease and prognosis of aTTP were identified in the guidelines presented by the pharmaceutical company. Taken together, the references cited by the pharmaceutical company suggest similarities regarding clinical aspects of adolescents and adults with aTTP. However, considering the limitations presented, it cannot be conclusively and with sufficient certainty assessed whether the disease and prognosis are comparable between adults and adolescents aged 12 years and older.

Comparability of efficacy and safety

Regarding the comparability of efficacy and safety of caplacizumab in adults and adolescents 12 years of age and older with aTTP, the pharmaceutical company uses a transfer of evidence from adults from the HERCULES study to the adolescent patients for the benefit assessment.

However, clinical trials in adolescents with aTTP are not available. Results on patient-relevant endpoints for the study population of adolescents (on the basis of which the transferability of therapy effects from adults to adolescents would be possible at all) are therefore lacking. Thus, a transfer of evidence of results on patient-relevant endpoints from the HERCULES study from adults to adolescents is not possible in the context of this benefit assessment.

As a result, the G-BA classified the extent of additional benefit of caplacizumab in the treatment of adolescents aged 12 years and older and weighing at least 40 kg who have an episode of acquired thrombotic thrombocytopenic purpura (aTTP) used in combination with plasmapheresis and immunosuppression as non-quantifiable. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of sentence SGB V, there is an additional benefit; however, this is non-quantifiable because the scientific data basis does not allow this.

Significance of the evidence

Because of the limitations of the evidence available, a hint for a non-quantifiable additional benefit can be derived with regard to the reliability of data.

2.1.3 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Cablivi with the active ingredient caplacizumab. Caplacizumab has been granted marketing authorisation as an orphan drug.

This assessment relates to the use of caplacizumab for the treatment of an episode of acquired thrombotic thrombocytopenic purpura (aTTP) in the following patient population:

Adolescents from 12 years weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP).

For adolescent patients with aTTP, no clinical trial data were submitted for the assessment of the additional benefit. Nevertheless, the pharmaceutical company aims at a transfer of evidence of the results of the HERCULES clinical study from adult patients with aTTP to adolescent patients with aTTP and a body weight of at least 40 kg.

The transfer of evidence from the adult HERCULES study to the study population of adolescents to be assessed as sought by the pharmaceutical company is not followed because results on patient-relevant endpoints for the study population of adolescents are missing. A transfer of evidence of results on patient-relevant outcomes from the HERCULES study from adults to adolescents is therefore not possible within the scope of this benefit assessment.

Because of the limitations of the evidence available, the reliability of data is assessed as a hint.

As a result, the G-BA classified the extent of additional benefit of caplacizumab in the treatment of adolescents aged 12 years and older and weighing at least 40 kg who have an episode of acquired thrombotic thrombocytopenic purpura (aTTP) used in combination with plasmapheresis and immunosuppression as non-quantifiable. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of sentence SGB V, there is an additional benefit; however, this is non-quantifiable because the scientific data basis does not allow this.

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 stated by the pharmaceutical company in the dossier. The calculation of the target population by the pharmaceutical company is mathematically comprehensible. In deriving the patient numbers, the pharmaceutical company essentially referred to the steps from the previous benefit assessment procedure on caplacizumab in the therapeutic indication on adult patients (resolution of 22 March 2019; in the justification of this resolution). Thus, the criticisms described for this procedure under patient numbers still apply.

Thus, the main criticisms of the derivation of patient numbers remain the potential exclusion of cases with aTTP that can be treated as partial inpatients or outpatients and the indication of the proportion of cases with aTTP based on retrospective epidemiological data collection, which is considered uncertain.

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 Cablivi (active ingredient: caplacizumab) at the following publicly accessible link (last access: 8 October 2020):

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

Treatment with caplacizumab should only be initiated and monitored by specialists who are experienced in the therapy of patients with thrombotic microangiopathy.

In accordance with EMA guidance on additional risk minimisation measures, a patient information card must be provided by the pharmaceutical company to all patients/caregivers who are expected to use caplacizumab. This patient information card is intended to convey the following primary concern:

- Inform physicians about medical blockade of the von Willebrand factor in order to reduce the risk of a major bleeding episode, especially in an emergency (e.g. an accident).

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 December 2020).

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Caplacizumab is used in combination with plasmapheresis and immunosuppression. Plasmapheresis and immunosuppression are standard therapies for acquired thrombotic thrombocytopenic purpura that are different for each individual patient and are given without the use of caplacizumab. Therefore, in the following, only the costs of caplacizumab and not the total treatment costs are presented.

Only whole packages are taken into account when determining costs.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Caplacizumab	Continuously, 1× before first plasmapheresis, 1× daily during plasmapheresis (total 5 days), and 30 days afterwards; if necessary, continuation up to a maximum of 65 days.	35–65[4]	1	35–65

4 For the lower limit of treatment duration, the median treatment duration with caplacizumab in the double-blind phase of the Hercules study is used (according to the product information Cablivi® Section 5.1). According to the product information of Cablivi®, the continuation of the daily administration caplacizumab is recommended if signs of residual immunologic disease are present at the end of the 30-day period following completion of daily plasma exchange. In the clinical development program, caplacizumab was administered daily for up to 65 days, which is assumed to be the upper limit of treatment duration.

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Caplacizumab	10 mg	10 mg	1 × 10 mg	35–65	35–65 × 10 mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Package 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					
Caplacizumab	7 PSI	€ 29,933.97	€ 1.77	€ 0.00	€ 29,932.20
Caplacizumab	1 PSI	€ 4,284.80	€ 1.77	€ 0.00	€ 4,283.03
Abbreviations: PSI = powder and solvent for solution for injection					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 December 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

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

The benefit assessment of the G-BA was published on 15 October 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 November 2020.

The oral hearing was held on 23 November 2020.

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 22 December 2020, and the proposed resolution was approved.

At its session on 7 January 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

5. Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	6 November 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	17 November 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 November 2020	Conduct of the oral hearing
Working group Section 35a	2 December 2020 16 December 2020	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 on Medicinal Products	22 December 2020	Concluding discussion of the draft resolution
Plenum	7 January 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 7 January 2021

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

Prof. Hecken