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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Danicopan (paroxysmal nocturnal haemoglobinuria with residual haemolytic anaemia, add-on to ravulizumab or eculizumab)

of 22 November 2024

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 danicopan on 1 June 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO. 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 28 May 2024.

Danicopan for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) 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 2 September 2024 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 G24-12) 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 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 danicopan.

[1] General Methods, version 7.0 from 19.09.2023. 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 Danicopan (Voydeya) in accordance with the product information

Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia.

Therapeutic indication of the resolution (resolution of 22 November 2024):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of danicopan as an add-on to ravulizumab or eculizumab is assessed as follows:

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

Justification:

The pharmaceutical company has submitted data from the completed, randomised-controlled, double-blind phase III ALPHA study for benefit assessment.

Adult patients with PNH and clinically significant extravascular haemolysis (EVH) who had been on stable treatment with eculizumab or ravulizumab for at least six months were enrolled.

The study comprises a screening period of 45 days, a 12-week double-blind, randomised-controlled phase (TP1), followed by a 12-week single-arm, open-label treatment phase (TP2) and 2 single-arm, open-label long-term therapy phases of 12 months each (LTE1 and LTE2).

For the TP1, patients were randomised into the intervention arm (danicopan; N = 57) and the control arm (placebo; N = 29) stratified according to transfusion history in the period of 6 months prior to screening (≤ 2 transfusions; > 2 transfusions), haemoglobin value at the time of screening (< 8.5 g/dl; ≥ 8.5 g/dl) and patients from Japan (yes; no). During TP1 and TP2, background therapy with ravulizumab or eculizumab was continued at a stable level.

The primary endpoint of the study was the change in Hb from baseline to week 12; additional endpoints were collected on symptomatology, health-related quality of life and adverse events.

For the ALPHA study, a pre-specified first data cut-off (28.06.2022) and, at the request of the regulatory authority, two further data cut-offs (20.09.2022 and 31.03.2023) were carried out. With its written statement, the pharmaceutical company also submitted the results of the 4th and final data cut-off from 22.03.2024. Based on the positive results of the first data cut-off, the TP1 was terminated prematurely on the recommendation of the Data Monitoring Committee and the study was unblinded. At the time of premature termination of TP1, 26 of the 29 patients (10.3%) in the control arm had completed TP1. According to the information provided by the pharmaceutical company in the written statement, this applies to 7 of the 57 patients (12.3%) in the intervention arm. The three subjects in the control arm who had not yet completed TP1 at this time were switched to danicopan before the end of TP1 and were excluded from the analyses of the endpoints in TP1 at the second and third data cut-offs presented in the dossier. The analyses of the efficacy endpoints presented in the dossier are

therefore based on a sub-population of the ITT population (mFAS). The pharmaceutical company submitted evaluations based on the ITT population for the 4th data cut-off from 24 March 2024 submitted with its written statement.

The evaluations of the ITT population for TP1 are used for this benefit assessment, as these are controlled data. For the endpoint categories of morbidity and quality of life, the results are based on the 4th data cut-off from 22.03.2024 submitted by the pharmaceutical company with its written statement. For the safety endpoints (including data on mortality), the results are based on the 3rd data cut-off from 31.03.2023 reported in the dossier, as this data cut-off already contains all final evaluations of the safety endpoints and the safety population corresponds to the ITT population.

Uncertainties of the ALPHA study

PNH is a chronic disease. Accordingly, as already stated in the G-BA's resolutions on ravulizumab and pegcetacoplan, a comparative study duration of at least 24 weeks is generally considered necessary by the G-BA in the therapeutic indication of PNH. Against this background, the ALPHA study randomised, controlled study phase TP1 duration of 12 weeks is considered too short overall to be able to derive reliable statements on the extent of the additional benefit from the available data.

In addition, further uncertainties arise from the premature discontinuation of TP1, as the surveys of some of the patients in the intervention and control arms were unblinded towards the end of TP1. Furthermore, unintentional unblinding of the study personnel cannot be ruled out, as the haemoglobin values of the patients were known to the treating study personnel.

The available data are therefore not assessable, especially due to the short TP1 duration (12 weeks), and are therefore unsuitable for quantifying the extent of the additional benefit.

Mortality

Overall survival was not collected as a separate endpoint in the ALPHA study. Fatalities were recorded as part of the assessment of the adverse events. Not a single death occurred in any study arm during the TP1.

Nevertheless, the results are not assessable against the background of the uncertainties of the ALPHA study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Morbidity

Change in Hb value from baseline to week 12

The endpoint of change in Hb value from baseline to week 12 was the primary endpoint of the ALPHA study.

The endpoint represents a laboratory parameter without direct reference to symptoms and is not patient-relevant per se. As this is the primary endpoint, it is presented additionally.

Transfusion independence

The endpoint of transfusion independence during TP1 describes the percentage of patients who did not require a transfusion from baseline to week 12.

According to the study protocol, a transfusion with red blood cell concentrates (RBC) was indicated if one of the following criteria was met:

- Hb value < 7 g/dl, regardless of the presence of clinical signs or symptoms

- Hb value < 9 g/dl with signs or symptoms of sufficient severity to justify transfusion.

Many patients in the present therapeutic indication require periodic transfusions. A long-term or sustainable avoidance of transfusions (transfusion independence or long-term transfusion avoidance) while maintaining a defined minimum value of haemoglobin represents a relevant therapeutic goal in the present therapeutic indication, with which a control of anaemia and anaemia-related symptoms is achieved, while avoiding transfusions. Thus, long-term transfusion independence may represent a patient-relevant endpoint in the present therapeutic indication. PNH is a chronic disease. Thus, no statements on the long-term avoidance of transfusions can be derived from a transfusion independence after only 12 weeks according to the comparator survey in the TP1. In addition, patients who met the transfusion criteria specified in the study protocol were categorised as transfused, regardless of whether a transfusion was administered. Subjects were therefore categorised as non-responders ("transfused") if they fulfilled the transfusion criteria but did not actually receive a transfusion.

The results for the endpoint of transfusion independence are therefore not assessable in the present case and thus not suitable for quantifying the extent of the additional benefit. The endpoint is only presented additionally.

Fatigue (FACIT-Fatigue)

In the ALPHA study, the fatigue perceived by the patients was recorded using the FACIT-Fatigue.

In its written statement on FACIT-Fatigue (as well as on the other patient-reported endpoints), the pharmaceutical company presented responder analyses for both improvement and deterioration.

The responder analysis for improvement did not show a statistically significant difference. The responder analysis for deterioration showed a statistically significant difference between the treatment arms in favour of danicopan.

Nevertheless, the results are not assessable against the background of the uncertainties of the ALPHA study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Symptomatology (EORTC QLQ-C30)

The symptomatology of the patients was assessed using the symptom scales of the EORTC-QLQ-C30 questionnaire in the ALPHA study.

The EORTC QLQ-C30 is a generic measurement tool for assessing the symptomatology and quality of life of patients with oncological diseases. The relevance of individual items of the questionnaire for the symptomatology of the present therapeutic indication is unclear. The symptom scales of the EORTC QLQ-C30 are therefore not used for the present assessment.

General health status (EQ-5D, visual analogue scale)

The health status of the patients was assessed in the ALPHA study using the visual analogue scale (VAS) of the EQ-5D questionnaire.

The responder analysis for improvement did not show a statistically significant difference. The responder analysis for deterioration showed a statistically significant difference between the treatment arms in favour of danicopan.

Nevertheless, the results are not assessable against the background of the uncertainties of the ALPHA study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Quality of life

Data on health-related quality of life from the ALPHA study are available using the functional scales and the global health status scale of the EORTC QLQ-C30 questionnaire.

The responder analyses for improvement showed a statistically significant difference in favour of danicopan in the physical functioning scale. The responder analyses for deterioration showed statistically significant differences between the treatment arms in favour of danicopan in the scales on physical functioning, role functioning and emotional functioning.

Nevertheless, the results are not assessable against the background of the uncertainties of the ALPHA study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Side effects

Adverse events (AEs) in total

AEs occurred in about 75% of patients in the intervention arm and about 62% of patients in the comparator arm. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs and therapy discontinuations due to AEs.

In the overall assessment, the results for the endpoint category of side effects are not assessable due to the uncertainties of the ALPHA study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Overall assessment

The results of the ALPHA study are available for the benefit assessment of danicopan as an add-on to ravulizumab or eculizumab for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia. In the 12-week, double-blind, randomised controlled phase (TP1) of the study, danicopan was compared with placebo (with stable background therapy with ravulizumab or eculizumab in each case).

PNH is a chronic disease. Accordingly, as already stated in the resolutions on ravulizumab and pegcetacoplan, a comparative study duration of at least 24 weeks is generally considered necessary by the G-BA in the therapeutic indication of PNH. Against this background, the ALPHA study TP1 duration of 12 weeks is considered too short overall to be able to derive reliable statements on the extent of the additional benefit from the available data.

In addition, further uncertainties arise as the TP1 was prematurely terminated and thus, the surveys of some of the patients in the intervention and control arms were unblinded towards the end of TP1. Furthermore, unintentional unblinding of the study personnel cannot be ruled out, as the haemoglobin values of the patients were known to the treating study personnel.

In summary, the available data on mortality, morbidity, quality of life and side effects do not allow quantification of the extent of the additional benefit of danicopan, especially due to the too short TP1 duration of 12 weeks.

As a result, a non-quantifiable additional benefit was identified for danicopan as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia, since the scientific data basis does not allow quantification.

Significance of the evidence

The present assessment is based on the results of the double-blind, randomised, controlled phase of the pivotal phase III ALPHA study.

The available results from the ALPHA study do not allow a quantification of the extent of the additional benefit in the overall assessment. The significance of the evidence is classified in the "hint" category.

2.1.3 Summary of the assessment

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

"Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia."

The pharmaceutical company submitted data from the pivotal phase III ALPHA study for the benefit assessment. In the double-blind, randomised controlled phase (TP1) of the study, danicopan was compared with placebo (with stable background therapy with ravulizumab or eculizumab in each case).

PNH is a chronic disease. Against this background, the TP1 duration of 12 weeks in particular is assessed as too short overall to be able to quantify the extent of the additional benefit. In addition, the ALPHA study is subject to further uncertainty.

Overall, it is therefore not possible to quantify the extent of the additional benefit of danicopan.

As a result, a non-quantifiable additional benefit is identified for danicopan since the scientific data basis does not allow quantification. 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 derived by IQWiG in the dossier assessment.

Although the pharmaceutical company's approach to deriving the patient numbers is mathematically plausible, the patient numbers stated by the pharmaceutical company is underestimated in the overall assessment due to the estimated percentages (7.4% to 21.3%) of clinically significant EVH. The reasons for this are a very low lower limit based on insufficient data and an operationalisation that deviates from the specifications in the product information, as well as a very low upper limit that is restricted to patients who were clinically stable after at least 6 months of eculizumab treatment.

Even taking into account the statements of clinical experts in the written statement procedure, according to which only 20% to 30% of patients experience a normalisation of the Hb value under terminal complement inhibition, the range of 25% to 50% derived by IQWiG

in the overall assessment is considered to be a better estimate for the percentage of clinically significant EVH.

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 Voydeya (active ingredient: danicopan) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 17 October 2024):

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

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 2024).

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				
Danicopan	Continuously, 3 x daily	365	1	365.0
Eculizumab	Continuously, 1 x every 12-16 days	22.8 – 30.4	1	22.8 – 30.4
Ravulizumab	Continuously, 1x every 56 days	6.5	1	6.5

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 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					
Danicopan	150 mg – 200 mg	450 mg – 600 mg	3 x 100 mg + 3 x 50 mg - 6 x 100 mg	365.0	1,095 x 100 mg + 1,095 x 50 mg - 2,190 x 100 mg
Eculizumab	900 mg	900 mg	3 x 300 mg	22.8 – 30.4	68.4 – 91.2 x 300 mg
Ravulizumab	3,300 mg	3,300 mg	3 x 1,100 mg	6.5	19.5 x 1,100 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 Section 130 and Section 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, from 15 years: http://www.gbe-bund.de

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					
Danicopan 100 mg | 50 mg	1 CMB	€ 8,355.10	€ 2.00	€ 476.57	€ 7,876.53
Danicopan 100 mg	180 FCT	€ 11,136.65	€ 2.00	€ 635.42	€ 10,499.23
Eculizumab	1 CIS	€ 5,586.75	€ 2.00	€ 318.47	€ 5,266.28
Ravulizumab	1 CIS	€ 17,043.19	€ 2.00	€ 972.75	€ 16,068.44
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; CMB = combo package					

LAUER-TAXE® last revised: 1 November 2024

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.

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

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 the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 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 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 Hilfstaxe.

2.5 Designation of 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 the assessed medicinal product

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product:

"Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for danicopan (Voydeya); Voydeya film-coated tablets; last revised: April 2024

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 28 May 2024, the pharmaceutical company submitted a dossier for the benefit assessment of danicopan 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 2 September 2024 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 23 September 2024.

The oral hearing was held on 7 October 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 29 October 2024.

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 12 November 2024, and the draft resolution was approved.

At its session on 22 November 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 August 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	1 October 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 October 2024	Conduct of the oral hearing
Working group Section 35a	15 October 2024 5 November 2024	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	12 November 2024	Concluding discussion of the draft resolution
Plenum	22 November 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 22 November 2024

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

Prof. Hecken