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)
Rucaparib (new therapeutic indication: ovarian, fallopian tube, or primary peritoneal cancer, maintenance treatment after first-line therapy)

of 6 June 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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 active ingredient rucaparib (Rubraca) was listed for the first time on 1 March 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 15 November 2023, rucaparib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 13 December 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient rucaparib with the

new therapeutic indication "Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in remission (complete or partial) following completion of first-line platinum-based chemotherapy" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 March 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, the G-BA decided on the question on whether an additional benefit of rucaparib compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG according to the General Methods was not used in the benefit assessment of rucaparib – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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 in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Rucaparib (Rubraca) in accordance with the product information

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 6 June 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in remission (complete or partial) following completion of first-line platinum-based chemotherapy; maintenance treatment

Appropriate comparator therapy for rucaparib as monotherapy:

A patient-individual therapy under selection of:

- bevacizumab
- olaparib
- niraparib
- olaparib in combination with bevacizumab

under consideration of:

- prior therapy
- the presence of a BRCA 1/2 mutation
- the presence of genomic instability

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to rucaparib, the active ingredients bevacizumab, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, melphalan, niraparib, olaparib, paclitaxel and treosulfan are available for treatment and subsequent maintenance treatment, depending on their authorisation status.

Medicinal products for the maintenance treatment of patients in a later line of therapy (platinum-sensitive relapse) and medicinal products with explicit maintenance treatment for second or subsequent line of therapy were not taken into account here.

on 2. A non-medicinal treatment cannot be considered in the present therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Olaparib: Resolutions of 21 September 2023 and 20 April 2023
- Niraparib: Resolution of 20 May 2021

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

According to current guidelines, chemotherapy with carboplatin in combination with paclitaxel is recommended as first-line or primary therapy for advanced ovarian cancer.

Platinum-based first-line chemotherapy should be followed by additional maintenance treatment of advanced ovarian cancer. In principle, the active ingredient bevacizumab,

PARP inhibitors or the combination of a PARP inhibitor with bevacizumab can be considered for maintenance treatment in accordance with current guidelines and the statements of the scientific-medical societies.

Maintenance treatment with bevacizumab is indicated if the primary therapy also included the use of bevacizumab. According to the bevacizumab product information, in this case, bevacizumab monotherapy is used following bevacizumab-containing primary treatment.

In addition, according to the current S3 guideline, bevacizumab in combination with a PARP inhibitor is recommended as maintenance treatment for patients who are in response following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose tumour has a positive homologous recombination deficiency (HRD) status defined by either a BRCA1/2 mutation and/or genomic instability. In this regard, only data for the active ingredient olaparib are available so far.

Accordingly, only olaparib in combination with bevacizumab has a marketing authorisation for the maintenance treatment of patients who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose tumour is associated with a positive homologous recombination deficiency (HRD) status. (HRD) positive status is defined here by either a BRCA1/2 mutation and/or genomic instability.

In addition to olaparib, the PARP inhibitor niraparib is also approved as a PARP inhibitor monotherapy for maintenance treatment of patients with advanced BRCA1/2 mutated, high-grade epithelial ovarian cancer, regardless of BRCA mutational status.

For olaparib in combination with bevacizumab, the G-BA identified a hint for a considerable additional benefit over bevacizumab in the benefit assessment by resolution of 20 April 2023.

No additional benefit was identified for olaparib as monotherapy compared with the appropriate comparator therapy in the benefit assessment by resolution of 21 September 2023.

By resolution of 20 May 2021, no additional benefit was identified for niraparib compared to the appropriate comparator therapy, against the background that no complete study data were available for the benefit assessment.

In view of the recommendations of the guidelines and the statements of the scientific-medical societies, it can be stated that no therapy option is generally preferable to other therapy options in this therapeutic indication. Instead, the treatment decision is based on the previous therapy, the presence of a BRCA1/2 mutation and the presence of genomic instability.

Against this background, the G-BA determines a patient-individual therapy by selecting bevacizumab, olaparib, niraparib and olaparib in combination with bevacizumab, taking into account the previous therapy, the presence of a BRCA1/2 mutation and the presence of genomic instability.

Olaparib as monotherapy and niraparib with regard to previous therapy in each case after a previous first-line platinum-based chemotherapy without bevacizumab are considered appropriate therapy options in the context of the patient-individual therapy determined as the appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

Editorial change to patient group

In the original version, the patient group was worded as follows:

"Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy; maintenance treatment"

In the present resolution, the wording of the patient group is adapted to the approved therapeutic indication and thus the following wording: "who are in response (complete or partial) following completion of first-line platinum-based chemotherapy" is changed to "who are in remission (complete or partial) following completion of first-line platinum-based chemotherapy".

This does not change the content and does not affect the present assessment.

2.1.3 Extent and probability of the additional benefit

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

For maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in remission (complete or partial) after first-line platinum-based chemotherapy, an additional benefit is not proven.

Justification:

The pharmaceutical company did not identify any relevant study for the assessment of the additional benefit of rucaparib in comparison with the appropriate comparator therapy. In this regard, IQWiG did not identify any relevant study in its review of the completeness of the study pool, in line with the information in the dossier. The pharmaceutical company excludes the possibility of an indirect comparison. The results of the ATHENA-MONO approval study were presented additionally by the pharmaceutical company in the dossier.

The ATHENA-MONO study is a multicentre, double-blind, randomised, 4-arm study in which rucaparib is compared with placebo in the relevant study arms.

The currently ongoing study enrolled adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who showed a response (complete or partial) following first-line platinum/taxane-based chemotherapy and cytoreductive operation. Patients should have received at least 4 to 8 cycles of platinum-based chemotherapy, of which at least 4 cycles of platinum-taxane combination therapy were given in first-line therapy. In the case of a partial response, the patient must have undergone at least 6 cycles.

The 538 patients enrolled were randomised in a 4:1 ratio to the intervention arm (rucaparib N = 427) and to the comparator arm (placebo N = 111).

Treatment with the study medication should be given for up to 2 years, until disease progression or discontinuation for other reasons, e.g. due to AE or at patient's discretion. Treatment could be continued for as long as 2 years even in the event of disease progression if the patients had a clinical benefit in the opinion of the investigator.

The ATHENA-MONO approval study presented additionally by the pharmaceutical company for the benefit assessment is a randomised, double-blind study in which rucaparib is compared with placebo. Thus, a comparison with the appropriate comparator therapy is not possible.

In summary, no adequate data are available to allow an assessment of the additional benefit, which is why an additional benefit of rucaparib in adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in remission (complete or partial) following completion of first-line platinum-based chemotherapy is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient rucaparib.

The therapeutic indication assessed here is as follows: " Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

As the appropriate comparator therapy, the G-BA determined a patient-individual therapy by selecting bevacizumab, olaparib, niraparib and olaparib in combination with bevacizumab, taking into account the previous therapy, the presence of a BRCA1/2 mutation and the presence of genomic instability.

The pharmaceutical company did not identify any relevant study for the assessment of the additional benefit of rucaparib in comparison with the appropriate comparator therapy. In this regard, IQWiG did not identify any relevant study in its review of the completeness of the study pool, in line with the information in the dossier. The results of the ATHENA-MONO approval study were presented additionally by the pharmaceutical company in the dossier.

In summary, no suitable data are available to allow an assessment of the additional benefit, which is why an additional benefit of rucaparib is not proven.

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).

Adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in remission (complete or partial) following completion of first-line platinum-based chemotherapy; maintenance treatment

The G-BA bases its resolution on IQWiG's calculation of patient numbers based on the information provided by the pharmaceutical company in the dossier. In this recalculation, a

maximum percentage of remission following subsequent first-line platinum-based chemotherapy was assumed for patients with no residual tumour after a previous operation. This value may also be lower, which could result in lower patient numbers.

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 Rubraca (active ingredient: rucaparib) at the following publicly accessible link (last access: 7 May 2024):

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

Treatment with rucaparib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with ovarian cancer.

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 May 2024).

The costs for the first year are presented.

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.

Administration of bevacizumab is limited to a maximum period of 15 months (including administration in combination with platinum treatment as part of first-line chemotherapy regimen). In 15 months, a total of 21.7 cycles every three weeks is possible. After deduction of the 6 cycles of bevacizumab in combination with the platinum treatment as part of first-line chemotherapy regimen, as mentioned in the product information, 15.7 cycles of bevacizumab in combination with olaparib remain in the present treatment setting. Only these are used for the calculation of the annual treatment costs.

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

The active ingredient bevacizumab is administered according to body weight. For doses according to body weight, the average body measurements from the official representative statistics “Microcensus 2021 – body measurements of the population” were applied. Taking into account the therapeutic indication, an average body weight of adult women is used for the calculation of consumption (69.2 kg)[1].

[1] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

As it is not possible to achieve the exact calculated dose per cycle with the commercially available dose strengths, in these cases the dose is rounded up to the next higher available dose.

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				
Rucaparib	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
A patient-individual therapy under selection of:				
Bevacizumab				
Bevacizumab	1 x every 21 days	15.7	1	15.7
Niraparib				
Niraparib	Continuously, 1 x daily	365.0	1	365.0
Olaparib				
Olaparib	Continuously, 2 x daily	365.0	1	365.0
Olaparib in combination with bevacizumab				
Olaparib	Continuously, 2 x daily	365.0	1	365.0
Bevacizumab	1 x every 21 days	15.7	1	15.7

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Rucaparib	600 mg	1,200 mg	4 x 300 mg	365.0	1,460 x 300 mg
Appropriate comparator therapy					
A patient-individual therapy under selection of:					
Bevacizumab					
Bevacizumab	15 mg/ kg BW = 1,038 mg	1,038 mg	2 x 400 mg + 3 x 100 mg	15.7	31.4 x 400 mg + 47.1 x 100 mg
Niraparib					
Niraparib	200 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Olaparib					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
Olaparib in combination with bevacizumab					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
Bevacizumab	15 mg/ kg BW = 1,038 mg	1,038 mg	2 x 400 mg + 3 x 100 mg	15.7	31.4 x 400 mg + 47.1 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 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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Rucaparib 300 mg	60 FCT	€ 2,592.43	€ 2.00	€ 144.76	€ 2,445.67
Appropriate comparator therapy					
Bevacizumab 100 mg	1 CIS	€ 397.02	€ 2.00	€ 21.35	€ 373.67
Bevacizumab 400 mg	1 CIS	€ 1,553.33	€ 2.00	€ 85.42	€ 1,465.91
Niraparib 100 mg	84 FCT	€ 5,955.07	€ 2.00	€ 336.80	€ 5,616.27
Olaparib 150 mg	112 FCT	€ 4,945.71	€ 2.00	€ 279.16	€ 4,664.55
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 May 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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

Other SHI benefits:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 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 do not add to the pharmacy sales price but follow the rules for calculation 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).

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 information 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:

Adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in remission (complete or partial) following completion of first-line platinum-based chemotherapy; maintenance treatment

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

References:
Summary of Product Characteristics (SmPC) for rucaparib (Rubraca); last revised: November 2023

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

At its session on 10 October 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 December 2023 the pharmaceutical company submitted a dossier for the benefit assessment of rucaparib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 14 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient rucaparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2024. The deadline for submitting statements was 5 April 2024.

The oral hearing was held on 22 April 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 28 May 2024, and the proposed resolution was approved.

At its session on 6 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 October 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	17 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	22 April 2024	Conduct of the oral hearing
Working group Section 35a	30 April 2024 15 May 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 May 2024	Concluding discussion of the draft resolution
Plenum	6 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 June 2024

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

Prof. Hecken