Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Rucaparib (maintenance treatment)

of 15 August 2019

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 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 shall pass a resolution 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 rucaparib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 March 2019. 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 26 February 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 3 June 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of rucaparib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of rucaparib.

In light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at 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 product information

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Maintenance treatment of adult patients with platinum-sensitive relapsed *high-grade* epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy

Olaparib *or* monitoring wait-and-see approach

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 Federal Joint Committee 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In terms of authorisation status, the active ingredients bevacizumab, cisplatin, carboplatin, cyclophosphamide, doxorubicin, liposomal doxorubicin (PLD), epirubicin, etoposide, gemcitabine, melphalan, niraparib, olaparib, paclitaxel, topotecan, trabectedin, and treosulfan are available.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

On 2. No non-medicinal treatments are considered.

On 3. Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V:

- Olaparib: Resolution of 6 December 2018
- Niraparib: Resolution of 7 June 2018

On 4. It is assumed that a platinum-sensitive, relapsed ovarian carcinoma is characterised by a response to a platinum-containing pretreatment with a relapse-free interval of at least 6 months. These include partially platinum-sensitive ovarian carcinomas with a relapse between 6 and 12 months after completion of platinum-containing chemotherapy.

In accordance with the current guidelines, systemic maintenance treatment with a poly(ADP-ribose) polymerase-1 (PARP) inhibitor may be considered for patients with relapse of high-grade serous epithelial ovarian cancer after response to platinum-containing relapse therapy. In addition to the PARP inhibitor rucaparib, which is currently under evaluation, the PARP inhibitors olaparib and niraparib also have corresponding marketing authorisation.

On 16 November 2017, the PARP inhibitor niraparib was authorised for maintenance treatment in adult patients with relapse of platinum-sensitive, poorly differentiated serous cancer of the ovaries or tubes or with primary peritoneal carcinoma in remission after platinum-based chemotherapy. The benefit assessment was based on limited evidence, which did not allow a valid and meaningful assessment of the results on the quantification of the additional benefit. The additional benefit for niraparib was classified as non-quantifiable on the basis of the criteria in Section 5, paragraph 7 AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease (resolution of 7 June 2018). The resolution was limited until 1 October 2020 because of immature data on overall survival. Overall, the significance of the active ingredient niraparib cannot currently be conclusively assessed. Niraparib is therefore not considered as an appropriate comparator therapy.

The PARP inhibitor olaparib was first approved on 16 December 2014 for maintenance treatment in adult patients with platinum-sensitive relapses of BRCA-mutated (germ line and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. On 8 May 2018, olaparib was approved for the therapeutic indication “Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy”. In its resolution of 6 December 2018, the G-BA identified a hint for a minor additional benefit in the benefit assessment for olaparib in this therapeutic indication. Compared with the appropriate comparator therapy of a monitoring wait-and-see approach, treatment with olaparib led to a moderate prolongation of overall survival with simultaneous disadvantages with regard to adverse events.

According to the German S3 guideline, which was published in January 2019, patients should be offered maintenance treatment with a PARP inhibitor (recommendation level B). In the same context, the recommendation is also weakened to “can be offered”. Accordingly, it cannot be deduced that the PARP inhibitor olaparib completely replaces the monitoring wait-and-see approach treatment standard observed to date.

Bevacizumab is authorised for the treatment of adult patients with a first platinum-sensitive relapse of epithelial ovarian, fallopian tube or primary peritoneal cancer. Bevacizumab is used either in combination with carboplatin and gemcitabine for six to ten treatment cycles or in combination with carboplatin and paclitaxel for six to eight treatment cycles and subsequently as a monotherapy until disease progression (maintenance treatment). The additional administration of bevacizumab could not significantly prolong overall survival in two Phase III studies, was associated with an

increased risk of adverse events, and is not defined as a standard therapy by relevant guidelines. Bevacizumab is therefore not included as an appropriate comparator therapy.

In the overall view, the G-BA has thus determined olaparib or monitoring wait-and-see approach as appropriate comparator therapy.

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

Change of the appropriate comparator therapy:

The appropriate comparator therapy was originally determined as follows:

The appropriate comparator therapy for rucaparib as monotherapy for maintenance treatment in adult patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy is

- monitoring wait-and-see approach.

Taking into account the resolution of the benefit assessment of olaparib of 6 December 2018, current guidelines, and the importance of olaparib in the statements of medical societies and experts in the procedure under discussion, this is also determined as an appropriate comparator therapy in addition to a monitoring wait-and-see approach.

This change in the appropriate comparator therapy neither effects the present assessment of additional benefit nor does it require a re-assessment of the benefit assessment.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit for rucaparib as monotherapy in the maintenance treatment in adult patients with platinum-sensitive, recurrent, high-grade epithelial ovarian, fallopian, or primary peritoneal carcinoma who are in remission (complete or partial) after platinum-based chemotherapy is not proven.

Justification:

The benefit assessment is based on the results of the double-blind randomised controlled ARIEL3 parallel study. In the ongoing study, rucaparib is compared with placebo.

Adult patients with a platinum-sensitive high-grade (grade 2 / 3) serous or endometrioid epithelial ovary, fallopian tube or primary peritoneal cancer were included. To be included, the patients must have already received at least two prior platinum-containing therapies, the last immediately before the start of the maintenance treatment with rucaparib. The response to the penultimate platinum-containing therapy is decisive for the definition of “platinum-sensitive”, which states that the disease must not have progressed earlier than 6 months after the last dose. The patients must have demonstrated a partial or complete response to the last platinum-containing therapy before the maintenance treatment. The last dose must not have been administered longer than 8 weeks before inclusion into the study. Moreover, prior treatment with a PARP inhibitor, including rucaparib, was not permitted.

The 564 patients included in the study were randomised to the rucaparib arm (N = 375) or the placebo arm (N = 189) at a ratio of 2:1. Stratification was performed dependent on homologous recombinant deficiency (HRD) status (tumour BRCA gene mutation-positive [tBRCA] / tumour BRCA gene mutation-negative but positive for other tumour mutations [non-tBRCA] / biomarker-negative, HRD-negative), time to disease progression after last dose of penultimate platinum chemotherapy before inclusion (6 to 12 months / > 12 months), and best response

(complete or partial) to last platinum chemotherapy before inclusion. Only patients with an ECOG status of 0 or 1 were included in the study. The mean age of patients was approximately 61 years at the time of inclusion. In more than 80% of the patients, the tumour was localised in the ovaries, and in about 95% of the patients, the tumour histology was serous. More than 60% of the patients had received two prior platinum-containing chemotherapies.

The patients are treated with rucaparib in accordance with the German authorisation status.

The ARIEL3 study aims to regularly examine patients for progression using imaging techniques. Taking into account guideline recommendations, which for patients in the present therapeutic indication primarily provide for a symptom-oriented approach with physical and gynaecological investigations instead of apparatus-based diagnostics and marker determination and which are used as the basis for implementing the monitoring wait-and-see approach, such regular examinations can reveal deviations in the implementation of the monitoring wait-and-see approach. However, in the study, the time between diagnosis of disease progression in both treatment arms is approximately 2 months. This suggests that diagnosis of disease progression using imaging procedures is not the only decisive factor relevant for ongoing patient therapy. Thus, the monitoring wait and see approach of the ARIEL3 study is considered to be adequate implementation of the appropriate comparator therapy.

Treatment is continued until disease progression in accordance with RECIST criteria, unacceptable toxicity, or withdrawal of informed consent. Following disease progression based on RECIST, patients and physicians can be unblinded on a case-by-case basis if a request to do so is made to the sponsor. A change from the comparator arm to the test arm is not possible.

The primary endpoint of the ARIEL3 Study is progression-free survival.

Two data cut-offs were evaluated. The first data cut-off of 15 April 2017 is the *a priori* planned primary analysis at the time 70% of patients in the tBRCA subgroup experienced a progression event based on RECIST. The second data cut-off of 31 December 2017 represents an interim analysis as part of the European authorisation process for the PFS2 and side effects endpoints. Consequently, the benefit assessment at hand uses the second data cut-off for the side effects endpoints and the first data cut-off for all other endpoints.

The study envisages a final analysis of the overall survival endpoint after 70% of the enrolled patients have died. Consulting EPAR, this is projected to occur in 2022. As part of the marketing authorisation, the pharmaceutical company was required to submit the data from this final analysis by the end of 2022.

Apart from the overall survival endpoint, endpoints are followed up 28 days after the last study medication is administered. In the rucaparib arm, the median duration of treatment is 8.3 months; in the placebo arm, it is 5.5 months.

Extent and probability of the additional benefit

Mortality

Overall survival

With regard to the endpoint overall survival, there is no statistically significant difference between rucaparib and a monitoring wait-and-see approach. However, because of the immature data basis, the result for this endpoint cannot be conclusively evaluated.

Morbidity

Progression-free survival (PFS)

Progression-free survival as assessed by the investigator (invPFS1) is the primary endpoint of the ARIEL3 study. This was defined as the time from randomisation to disease progression (+1 day) according to RECIST v1.1 criteria or to death of any cause, whichever occurs first.

With regard to invPFS1, there is a statistically significant difference between the two treatment arms (hazard ratio (HR): 0.365; [95% confidence interval (CI) 0.295; 0.451]; p value < 0.0001). Under rucaparib treatment, this event occurred after 10.8 months (median) compared with 5.4 months in the comparator arm.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging techniques (according to RECIST v1.1). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Health status

In the ARIEL3 study, health status is measured using the visual analogue scale (VAS) of EQ-5D. In the dossier, the pharmaceutical company presented, on the one hand, data on the mean change in health status from the individual time-point under consideration to the start of study. On the other, it presents *post hoc* defined responder analyses based on a deterioration of 7 points compared to the baseline.

The IQWIG did not take into consideration the responder analyses in its dossier evaluation. This is justified by the fact that no MID can be derived from the work cited. Instead, the mean change compared with the start of study were used. The IQWiG considered the mean change to cycle 3, because the results cannot be used at later points in time because of the high proportion of patients not included in the evaluations (> 30%).

In view of the fact that there are general advantages in using MID-based responder analyses to clinically evaluate effects over analyses of differences in mean values and in view of the fact that the validation study in question has already been used in earlier evaluations, in the present assessment, the G-BA has decided to use the responder analyses to assess the effects on symptomatology.

The responder analysis with the underlying MID of 7 points shows no statistically significant difference between rucaparib and a monitoring wait-and-see approach (HR: 1.26; [95% CI 0.99; 1.60]; p = 0.056).

Symptomatology

In contrast to the assessment of the pharmaceutical company, the data collected using the FOSI-18 DRS-P sub-scale (Disease-related Symptoms Sub-scale - physical of the Functional Analysis of Cancer Therapy Ovarian Symptom Index-18) are not assigned to the quality of life category but rather to the endpoint symptomatology.

In addition to mean change data from the start of study at the respective time of measurement, the pharmaceutical company also presented responder analyses with regard to a first deterioration of 4 points from baseline. The MID was defined *a priori* as 4 points. However, the criterion on which the derivation of MID was based (10% of the total width of the scale) is not suitable for deriving an adequate MID as would be possible using primarily anchor-based methods.

As a result, data on the mean difference was taken into consideration. This analysis considers the mean change at the end of treatment cycle 3 in comparison to the start of study because a high proportion of patients were not considered in evaluations after treatment cycle 3.

The mean difference data show a statistically significant difference to the detriment of rucaparib, whereby the confidence interval of Hedges’ g is uniformly beyond the irrelevance range (mean difference −2.3 [3.1; −1.5]; p < 0.001; Hedges’ g: −0.57 [−0.78; −0.37).]

Overall, for the morbidity category, there is a disadvantage of rucaparib compared with a monitoring wait-and-see approach.

Quality of life

The ARIEL3 study does not collect data on quality of life.

Side effects

Adverse events (AEs) in total

The results for the endpoint Adverse events in total are presented only on a supplementary basis.

In the rucaparib arm, each patient experienced an adverse event; in the placebo arm, 96.3% of patients experienced an adverse event.

Serious adverse events (SAEs)

With regard to the SAE endpoint, there is no statistically significant difference between the two treatment arms. In the test arm 22.3% of the patients suffered from an SAE; in the control arm, 10.6%.

Severe AEs (CTCAE grade ≥ 3)

There is a statistically significant difference to the detriment of rucaparib (HR: 4.33; [95% CI: 2.93; 6.40]; $p < 0.001$). The patients in the rucaparib arm experienced an AE 36.9 months (median) earlier.

Withdrawal because of AEs

The rucaparib arm shows a statistically significant disadvantage (HR: 5.55; [95% CI: 2.00; 15.40]; $p = 0.001$) with respect to therapy discontinuation because of AEs

Specific AEs

There is a statistically significant difference to the detriment of rucaparib with regard to the endpoints “General disorders and administration site conditions (AE, SOC)”, “Gastrointestinal disorders (AE, SOC)”, “Photosensitivity response (AE, PT)”, “Taste disorder (AE, PT)”, and “Blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3)”. With regard to the endpoints “Myelodysplastic syndrome (AE, PT)” and “Acute myeloid leukaemia (AE, PT)”, there is no statistically significant difference between the two therapy arms. For the endpoint “Musculoskeletal, connective tissue and bone disorders (AE, SOC)”, there is a significant advantage under rucaparib therapy.

In summary, in the side effects category rucaparib is associated by a wide margin with disadvantages compared to the wait-and-see monitoring approach. These occur, in particular, in the serious AE and discontinuation because of AEs.

Overall assessment/conclusion

Data on mortality, morbidity and adverse reactions are available for the assessment of the additional benefit of rucaparib as maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

With regard to the mortality endpoint, there is no difference between rucaparib and a monitoring wait-and-see approach; however, this endpoint cannot be conclusively assessed on the basis of the available data, which can still be classified as immature.

With regard to the morbidity category, no difference in health status surveyed via EQ-5D VAS was observed between the treatment arms. However, a statistically significant, relevant disadvantage in symptomatology was evaluated as mean differences over the FOSI-18 DRS-P sub-scale. Overall, rucaparib is associated with disadvantages in the morbidity category.

There are disadvantages regarding severe AEs (CTCAE grade ≥ 3) as well as withdrawal because of AEs. With the exception of the endpoint "Musculoskeletal, connective tissue and

bone disorders (AE, SOC)", rucaparib is exclusively associated with disadvantages in the side-effects category, also in detailed outcomes

In the overall view, in the absence of data on quality of life, the findings were universally disadvantageous in the morbidity category and predominantly disadvantageous in the side-effects category, which, however, could not be conclusively assessed because the immature overall survival endpoint data.

Overall, an additional benefit for rucaparib as maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy is not proven.

2.1.4 Limitation of the period of validity of the resolution

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

The resolution is based on the data cut-off of 15 April 2017 and the data cut-off of 31 December 2017 for the endpoints of the category side effects. With regard to the overall survival endpoint, the data are not yet classified as conclusively assessable at this point.

The pharmaceutical company is required to submit data from the final overall survival analysis to the EMA by 31 December 2022.

In view of the fact that further clinical data that may be relevant for the benefit assessment of rucaparib in the present indication are expected, the period of validity of the present resolution is justifiable.

Conditions of the limitation

The dossier to reassess the additional benefit after expiry of the limitation period should include the results of the final overall survival analysis and of all other patient-relevant endpoints from the ARIEL3 study.

A limitation of the resolution until 1 April 2023 is considered to be appropriate.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3 paragraph 1 number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of rucaparib shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of rucaparib (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment of rucaparib can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1 paragraph 2 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Rubraca with the active ingredient rucaparib.

Rubraca has been given a conditional marketing authorisation.

The therapeutic indication assessed here is as follows:

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The G-BA identified olaparib or a monitoring wait-and-see approach as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented the results of the ARIEL3 study in which rucaparib is compared with placebo. The comparator arm is evaluated as a sufficient approximation to the appropriate comparator therapy, a monitoring wait-and-see approach.

There is no statistically significant difference in overall survival. However, the data provided are considered immature.

There is a relevant disadvantage with regard to symptomatology measured using the FOSI-18 DRS-P sub-scale. There are no differences in health status based on EQ-5D VAS.

Data on quality of life are not collected in the ARIEL3 study.

In the category side effects, there are predominantly disadvantages to the detriment of rucaparib, in particular with regard to severe AEs (CTCAE grade ≥ 3) and withdrawal because of AEs.

Therefore overall, there are only disadvantages to the detriment of rucaparib compared with appropriate comparator therapy, a monitoring wait-and-see approach. In view of the currently immature data on overall survival, the results cannot be conclusively assessed.

The resolution is limited until 1 April 2023.

For the reassessment, data on all patient-relevant endpoints of the final overall survival analysis from the ARIEL3 study should be presented.

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 IQWiG considers the derivation of patient numbers by the pharmaceutical company to be plausible but classifies it as uncertain. This is due to a partly weak data basis as well as an incomprehensible methodical approach.

In the absence of a better data basis and in order to enable a consistent consideration of patient numbers taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, the G-BA considers it appropriate to draw on the patient numbers stated in the resolution on niraparib (resolution of 7 June 2018). These are also the basis for the benefit assessment of olaparib (resolution of 6 December 2018).

These are afflicted with uncertainties, as the extent and course of the uncertainty could not be determined because of the large number of proportional values used and combined calculation steps. However, a recalculation by the IQWiG in the benefit assessment procedure for niraparib lends credence to the pharmaceutical company's figures for niraparib, which were of the same order of magnitude and assume a mean survival of 2–3 years in the field of application under consideration.

Furthermore, the present finding on patient numbers took into account that patients with non-serous histology are within the scope of the therapeutic indication of rucaparib but not in the scope of the therapeutic indication of niraparib. Because this sub-population represents only a small proportion of patients in the current therapeutic indication, this uncertainty is considered supportable.

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: 5 July 2019):

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

Only specialists in internal medicine, haematology and oncology with experience treating patients with ovarian cancer, and specialist in gynaecology and other doctors from other specialisms participating in the oncology agreement may initiate and monitor treatment with rucaparib.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is expected. The EMA will evaluate new information on this medicinal product at least annually and update the product information if necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2019).

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	continuous, 2 × daily	365	1	365
Appropriate comparator therapy				
Olaparib	continuous, 2 x daily	365	1	365
Monitoring wait-and-see approach	not quantifiable			

Usage and 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.

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Rucaparib	600 mg	1200 mg	4 × 300 mg	365	1460 × 300 mg
Appropriate comparator therapy					
Olaparib	300 mg	600 mg	4 × 150 mg	365	1460 × 150 mg
Monitoring wait-and-see approach	not quantifiable				

Costs:

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with 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 on the basis of consumption. Having determined the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Rucaparib	60 FCT	€ 4,647.57	€ 1.77	€ 262.15	€ 4,383.65
Appropriate comparator therapy					
Olaparib	112 FCT	€ 6,730.08	€ 1.77	€ 381.08	€ 6,347.23
Monitoring wait-and-see approach	not quantifiable				
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

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 usual expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 11 September 2018.

On 26 February 2019, 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 1, sentence 2 VerfO.

By letter dated 26 February 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 XYZ.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 May 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 3 June 2019. The deadline for submitting written statements was 24 June 2019.

The oral hearing was held on 9 July 2019.

On 7 August 2019, IQWiG submitted a new version of the IQWiG dossier evaluation to the G-BA. Version 1.1 of 7 August 2019 replaces version 1.0 of the dossier evaluation of 29 May 2019. The evaluation result was not affected by the changes in version 1.1 compared with version 1.0.

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 6 August 2019, and the proposed resolution was approved.

At its session on 15 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	11 September 2018	Determination of the appropriate comparator therapy
Working group Section 35a	3 July 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	9 July 2019	Conduct of the oral hearing
Working group Section 35a	17 July 2019 31 July 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal product	6 August 2019	Concluding discussion of the proposed resolution
Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

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

Prof Hecken