Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Niraparib (Reassessment after the deadline (Ovarian, fallopian tube or primary peritoneal cancer))

of 15 July 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient niraparib (Zejula) was listed for the first time on 15 December 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Zejula for the treatment of ovarian, fallopian tube or primary peritoneal cancer is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In its session on 12 July 2018, the G-BA decided on the benefit assessment of niraparib in the therapeutic indication "Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy." in accordance with Section 35a of the German Social Code, Book V (SGB V).

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 50 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 27 June 2019, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V due to exceeding the € 50 million turnover limit. The pharmaceutical company submitted in due time 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 6 VerfO on 15 October 2019. For the resolution of 2 April 2020 made by the G-BA in this procedure, a limitation of 1 October 2020 was pronounced. By resolution dated 20 August 2020, the period of validity of the resolution was extended to 1 February 2021.

In accordance with Section 4, paragraph 3 paragraph 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product niraparib recommences when the deadline has expired. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 1 February 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 May 2021 on the G-BA website (www.g-ba.de), therefore 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 niraparib compared to 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 niraparib.

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 for niraparib (Zejula) according to the product information

Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary

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

peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 15.07.2021):

"see approved therapeutic indication"

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 serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy

Appropriate comparator therapy:

- 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 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 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, in addition to niraparib, the available active ingredients are bevacizumab, cisplatin, carboplatin, cyclophosphamide, doxorubicin, liposomal

doxorubicin (PLD), epirubicin, etoposide, gemcitabine, melphalan, olaparib, paclitaxel, rucaparib, topotecan, trabectedin and treosulfan.

on 2. No non-medicinal treatments can be considered.

on 3. The following resolutions and guidelines of the G-BA are available for medicinal product treatment in the present therapeutic indication:

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

- Rucaparib: Resolution of 15 August 2019
- Olaparib: Resolution of 6 December 2018
- Niraparib: Resolution of 7 June 2018

on 4. 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 health care provision.

The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies.

For the present therapeutic indication, platinum-sensitive relapsed ovarian cancer is considered to be based on a response to platinum-containing pretreatment with a relapse-free interval of at least six months. This includes partially platinum-sensitive ovarian cancers with a relapse between six and twelve months after completion of platinum-containing chemotherapy.

According to the current German S3 guideline (2020[2]), systemic maintenance therapy with a poly(ADP-ribose) polymerase 1 (PARP) inhibitor may be considered for patients with relapse of high-grade serous epithelial cancer of the ovary after response to platinum-containing relapse therapy. In addition to the PARP inhibitor niraparib, which is being evaluated here, the PARP inhibitors olaparib and rucaparib have a corresponding marketing authorisation. Niraparib is approved as an orphan drug for the treatment of a rare condition.

The PARP inhibitor olaparib was initially approved on 16 December 2014, for the maintenance treatment of adult patients with platinum-sensitive relapse of BRCA-mutated (germline and/or somatic) *high-grade* serous epithelial ovarian, fallopian tube or primary peritoneal cancer who respond to platinum-based chemotherapy. On 8 May 2018, olaparib was approved for the therapeutic indication "Lynparza is s 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." In its resolution of 6 December 2018, the G-BA determined a hint for a minor additional benefit in the benefit assessment of olaparib in this therapeutic indication. Compared to the appropriate comparator therapy with monitoring wait-and-see approach, treatment with olaparib led to a moderate prolongation of overall survival with concomitant adverse events.

2 S3 guideline diagnostics, therapy and aftercare of malignant ovarian tumours. Version 4.0-March2020 AWMF Register Number: 032/035OL.

The PARP inhibitor rucaparib was approved on 23 May 2018, is indicated as monotherapy for the maintenance treatment of adult patients with platinumsensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. In its resolution of 15 August 2019, the G-BA did not determine any additional benefit in the benefit assessment of rucaparib in this therapeutic indication compared to monitoring wait-and-see approach. The resolution is valid until 1 April 2023. Rucaparib thus represents a further treatment option approved for the present therapeutic indication, which is still relatively new in the care of patients and whose therapeutic significance cannot yet be conclusively assessed.

According to the current German S3 guideline, patients with relapse of high-grade ovarian cancer "should" be offered maintenance therapy with a PARP inhibitor after response to platinum-containing relapse therapy. Furthermore, in the body text of the guideline, the recommendation is weakened to "may be offered". Accordingly, it cannot be inferred that the PARP inhibitor olaparib completely replaces the previous therapy standard "monitoring wait-and-see approach".

In addition, bevacizumab is approved for treatment of adult patients with first relapse of platinum-sensitive 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 monotherapy until disease progression (maintenance therapy). The additional administration of bevacizumab did not significantly prolong overall survival in two phase III studies, was associated with an increased risk of side effects, and is not defined as a standard therapy by relevant guidelines. Bevacizumab is therefore not included in the appropriate comparator therapy.

Overall, the G-BA thus determined olaparib or monitoring wait-and-see approach as equally appropriate comparator therapies.

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

2.1.3 Extent and probability of the additional benefit

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

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

Justification:

The pharmaceutical company submitted an adjusted indirect comparison via the bridge comparator placebo versus olaparib to demonstrate an additional benefit of niraparib.

The G-BA notes in this regard that a direct comparison of niraparib versus the alternative appropriate comparator therapy "monitoring wait-and-see approach", operationalised as placebo, would also have been possible through the NOVA study, which regularly shows a higher certainty of results and would also have allowed statements on morbidity and quality of life under niraparib.

For the adjusted indirect comparison, the RCTs NOVA and NORA were cited on the side of niraparib and the two RCTs SOLO2 and Study 19 on the side of olaparib. The NORA study was not used for this evaluation. The NORA study is a niraparib versus placebo comparative phase III study in the therapeutic indication conducted in China and not by the pharmaceutical company itself. It is noted that even with the inclusion of the NORA study in the indirect comparison, the result for the endpoint overall survival would not change. For further endpoints, no results from the NORA study are available that can be used for indirect comparison.

NOVA study

The NOVA study is a multicenter, randomised, double-blind, controlled phase III study comparing niraparib to placebo in two independent cohorts. The study included adult patients with a platinum-sensitive relapsed ovarian cancer who are in response, completely or partially, to prior platinum-containing chemotherapy. Tumour histology had to be either high-grade (or grade 3) serous or high-grade predominantly serous, or the tumour had to have a known BRCA germline mutation. Furthermore, patients should have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 for inclusion.

A total of 553 patients were included in the NOVA study. Here, the gBRCAmut cohort included patients with a germline BRCA mutation (n=203) and the non-gBRCAmut cohort included patients without a germline BRCA mutation (n=350). Patients were randomised in a 2:1 ratio and assigned to treatment with niraparib (N = 372 (gBRCAmut: 138; non-gBRCAmut: 234)) or placebo (N = 181 (gBRCAmut: 65; non-gBRCAmut: 116)). It was stratified by time to disease progression after the last dose of penultimate platinum-containing chemotherapy before time of enrolment (> 6 to 12 months vs > 12 months), response during the last platinum-containing chemotherapy (complete vs partial), and use of bevacizumab in conjunction with the penultimate or last platinum-containing therapy regimen (yes vs no).

Treatment with the study medication was given until disease progression or discontinuation for other reasons, e.g. due to AE or patient choice. However, patients were allowed to continue treatment even despite disease progression if, in the opinion of the investigator, the patients had clinical benefit. A change of patients from the control arm to the intervention arm was not planned in the NOVA study. Patients who were unblinded to determine subsequent therapy were afterwards excluded from the study.

NOVA was conducted in 128 study sites in Asia, Europe and North America. The study started in August 2013. For the benefit assessment, there is an a priori planned primary data cut-off from 30.05.2016 and final overall survival data cut-off from 01.10.2020 available.

Study 19

Study 19 is a multicenter, double-blind, randomised controlled study comparing olaparib with placebo. The study took place from August 2008 to May 2016 and has therefore already been completed. Adult patients with a platinum-sensitive relapse of high-grade serous ovarian cancer who had responded completely or partially to prior platinum-containing chemotherapy

were included. In Study 19, patients were included regardless of their BRCA mutation status. However, this was determined after the primary data cut-off. Patients should have a performance status according to ECOG-PS of 0 or 2 prior to the start of the study.

The 265 included patients were randomised 1:1 to the olaparib arm (N=136) and to the placebo arm (N=129). It was stratified by time to disease progression after the last dose of penultimate platinum-containing chemotherapy before study inclusion (> 6 to 12 months vs > 12 months), objective response to last platinum-containing chemotherapy before time of enrolment (complete vs partial), and Jewish ancestry (yes vs no; due to increased BRCA mutation prevalence in this population).

Treatment with study medication continued until disease progression, discontinuation due to AE, or withdrawal of informed consent. However, patients were allowed to continue treatment even despite disease progression if, in the opinion of the investigator, the patients had clinical benefit. A change of patients from the control arm to the intervention arm was not allow in Study 19. Since olaparib was already available in some study centres at the time of study conduct, some patients from the placebo arm nevertheless received olaparib as a subsequent therapy.

The Study 19 was conducted in 82 study centres in Asia, Australia, Europe and North America.

For Study 19, data are available for all patient-relevant outcomes except health-related quality of life for the 6th or final data cut-off on 9.05.2016. Data on health-related quality of life are only available from the 1st data cut-off as their assessment was subsequently discontinued. For the present benefit assessment, the 6th data cut-off was used.

SOLO2 study

The SOLO2 study is a multicenter, double-blind, randomised controlled study comparing olaparib to placebo. The international study included adult patients with platinum-sensitive relapse of high-grade serous ovarian cancer who had responded to prior platinum-containing chemotherapy. In SOLO2, only patients with BRCA mutation were included. For inclusion, patients should have a performance status according to ECOG-PS of 0 or 1.

The 295 included patients were randomised 2:1 to the olaparib arm (N=196) and to the placebo arm (N=99). It was stratified by response to last platinum-containing chemotherapy (complete vs partial) and by time to disease progression after penultimate platinum-containing chemotherapy before time of enrolment (> 6 to 12 months vs > 12 months).

In addition to the main cohort used here, there is also a Chinese cohort with 32 patients, which is not included because no relevant additional information can be expected from it.

Treatment with study medication continued until disease progression, discontinuation due to AE, or withdrawal of informed consent. However, patients were allowed to continue treatment even despite disease progression if, in the opinion of the investigator, the patients had clinical benefit. A change of patients from the control arm to the intervention arm was not allow in SOLO2 study. Since olaparib was already available in some study centres at the time of study conduct, some patients from the placebo arm nevertheless received olaparib as a subsequent therapy.

The SOLO2 study was conducted in 119 study sites in Asia, Australia, Europe, North and South America. For the study started in August 2013, an a priori planned primary data cut-off is available from 19.09.2016 and the final overall survival data cut-off is available from 03.02.2020.

On the indirect comparison

As there were no major differences between the NOVA, SOLO2 and Study 19 with regard to the included patient populations and study conduct, the studies are considered to be sufficiently similar overall for an adjusted indirect comparison.

As the adjusted indirect comparison submitted by the pharmaceutical company in the dossier includes the results of the NORA study, the IQWiG calculated another adjusted indirect comparison in its dossier assessment themselves, taking into account the studies NOVA, Study 19 and SOLO2. Thereby, the SOLO2 and Study 19 studies were considered as a meta-analytic summary.

On the implementation of the requirements for reassessment:

According to the justification for the resolution, the reason for the time limitation of the resolution was that a small number of overall survival events from the NOVA study were available at the time of the assessment. The limitation enables the expected final results from the NOVA study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

With the data cut-off from the 01.10.2020 final analyses of the NOVA study were performed and submitted for evaluation after ≥ 66% of patients died.

Extent and probability of the additional benefit

Mortality

Because the results for the endpoint overall survival of the final data cut-off of the NOVA study are potentially highly biased, the potentially low-biased results for the endpoint overall survival based on the primary data cut-off (30.05.2016) were used to perform the adjusted indirect comparison for this endpoint.

For the endpoint overall survival, the adjusted indirect comparison showed no statistically significant difference between niraparib and olaparib.

No additional benefit is identified for the endpoint overall survival.

Morbidity

Progression-free survival (PFS)

No usable data on progression-free survival are available for the adjusted indirect comparison.

Health status (EQ-5D, visual analogue scale)

No usable data are available for the endpoint health status, measured by the VAS of the EQ-5D, as different follow-up strategies were used in the studies for this endpoint.
Therefore, no usable data are available for the endpoint health status.

Symptomatology

In the NOVA study, symptomatology was assessed using the FOSI-8 symptom score, which is part of the FACT-O questionnaire. On the olaparib studies' side, evaluations of FOSI-8 are only available with a high risk of bias across endpoints from Study 19. Since at least one study with sufficient reliability of data should be available on each side of the comparison for an adjusted indirect comparison, the results cannot be used for the indirect comparison.
Thus, no usable data are available with regard to symptomatology.

Quality of life

The total score of the disease-specific questionnaire FACT-O was used to assess health-related quality of life in the SOLO2 and Study 19 studies, but not in the NOVA study. Therefore, insufficient data are available for an indirect comparison.
Thus no usable data on health-related quality of life are available.

Side effects

For the endpoint category adverse events, the results of the final data cut-off of the NOVA study were used for the adjusted indirect comparison.

Adverse events (AEs)

Adverse events occurred at least once in almost all patients in the treatment groups of the studies. Therefore, the results were only presented additionally.

Serious AEs (SAE)

For the endpoint SAEs, there are potentially highly biased results on the niraparib side of the indirect comparison. Thus, the conditions for deriving reliable conclusions from an adjusted indirect comparison are not met here either.

Severe AEs

On the niraparib side of the adjusted indirect comparison, only the results with endpoint-related high risk of bias of the NOVA study are available. The prerequisites for being able to derive statements on additional benefit from an adjusted indirect comparison are therefore not fulfilled.
However, in the adjusted indirect comparison with olaparib, there is a large statistically significant effect to the disadvantage of niraparib. Thus, despite the high endpoint-specific risk of bias in the NOVA study, there is a sufficiently high qualitative certainty of results to be able to interpret the present effect.
However, it remains uncertain to what extent this effect would be influenced by the weight-adjusted reduction of the initial dose. This was also pointed out in the written statement procedure. In addition, the severe AEs in detail are predominantly blood count changes that are not symptomatic per se.

Discontinuation because of AEs

For the endpoint discontinuation due to AE, only results with limited certainty of outcome are available on the niraparib edge of the indirect comparison. Thus, the prerequisites for making

statements on the additional benefit from an adjusted indirect comparison are not fulfilled here either.

Specific AEs

No usable data are available for the specific AEs of particular importance, as different follow-up strategies were used in the studies for these endpoints. For the specific AE pneumonitis, there are too few events to calculate an adjusted indirect comparison.

In the overall view of the results on side effects, results from the adjusted indirect comparison that allow sufficient reliable conclusions are only available for the endpoint Severe AEs. Thus, no conclusions can be made about serious AEs, specific AEs and discontinuations due to AEs.

Although the negative effect of niraparib compared to olaparib in the severe AEs cannot be completely questioned by potential biases, its significance, magnitude and therapeutic importance, taking into account the lack of usable data for other endpoints in the category side effects and considering the statements of the medical societies, is not considered sufficient to infer a lower overall benefit of niraparib compared to olaparib with regard to side effects.

<u>Overall assessment/conclusion</u>

For the assessment of the additional benefit of niraparib, an adjusted indirect comparison of niraparib (NOVA study) with olaparib (SOLO2 study and Study 19) via the bridge comparator placebo is available. This adjusted indirect comparison yields results for the endpoint categories mortality and side effects.

For the endpoint overall survival, the adjusted indirect comparison shows no statistically significant difference between niraparib and olaparib. No additional benefit is determined for the endpoint overall survival.

No usable data are available for the endpoint categories morbidity and health-related quality of life.

In the endpoint category side effects, no usable data are available for the endpoints SAE, discontinuation due to AEs and for the specific AEs.

Based on the adjusted indirect comparison for the endpoint severe AE (CTCAE grade ≥ 3), there is a statistically significant effect to the disadvantage of niraparib compared to olaparib. It cannot be assumed that this large effect to the disadvantage of niraparib can be completely challenged by potential biases.

In the overall view, results from the adjusted indirect comparison are only available for the endpoint categories mortality and side effects.

These show only one disadvantage for treatment with niraparib compared to olaparib.

Although the negative effect of niraparib compared to olaparib in the severe AEs cannot be completely questioned due to potential bias, its significance, magnitude and therapeutic importance, taking into account the lack of usable data for other endpoints in the category side effects as well as taking into account the statements of the medical societies, is not considered sufficient to infer a lower overall benefit of niraparib compared to olaparib in the

overall assessment. It is therefore concluded that an additional benefit is not proven for niraparib compared with olaparib.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient niraparib due to the expiry of the limitation of the resolution of 2 April 2020.

The therapeutic indication assessed here is as follows: niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

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

For the evaluation, the pharmaceutical company presents an adjusted indirect comparison between niraparib and olaparib via the bridging comparator placebo. For this indirect comparison, the NOVA study was used for niraparib and the Study19 and SOLO2 studies for olaparib.

For the endpoint overall survival, the indirect adjusted comparison shows no statistically significant difference between niraparib and olaparib.

No usable data are available for the endpoint categories morbidity and health-related quality of life.

In the endpoint category side effects, no usable data are available for the endpoints SAE, discontinuation due to AEs and for the specific AEs.

Based on the adjusted indirect comparison, there is a statistically significant effect for the endpoint severe AE (CTCAE grade ≥ 3) to the disadvantage of niraparib compared to olaparib. It cannot be assumed that this large effect to the disadvantage of niraparib can be completely challenged by potential biases.

In the overall view, results from the adjusted indirect comparison are only available for the endpoint categories mortality and side effects.

These show only one disadvantage for treatment with niraparib compared to olaparib.

Although the negative effect of niraparib compared to olaparib in the severe AEs cannot be completely questioned due to potential bias, its significance, magnitude and therapeutic importance, taking into account the lack of usable data for other endpoints in the category side effects as well as taking into account the statements of the medical societies, is not considered sufficient to infer a lower overall benefit of niraparib compared to olaparib in the overall assessment. It is therefore concluded that an additional benefit is not proven for niraparib compared with olaparib.

2.2 Number of patients or demarcation of patient groups eligible for treatment

approx. 700 to 1,000 patients

The information on the number of patients is based on the target population in statutory health insurance (SHI).

IQWiG considered the derivation of patient numbers by the pharmaceutical company to be largely mathematically comprehensible, however, due in particular to the lack of restriction to patients in a 2nd therapy line (platinum-based) as overestimated. Due to the methodological approach, further uncertainties arose in the different steps of the derivation. In addition, case numbers of patients with cancer of the fallopian tubes or primary peritoneal cancer, which are not recorded using the ICD-10 code C 56, were not taken into account.

Therefore, a recalculation was performed based on the derivation of the pharmaceutical company. Additional consideration was given to the approximately 450 cases of malignant tumours of the fallopian tubes and approximately 300 cases of malignant tumours of the peritoneum annually[3]. Furthermore, in step 7, the target population was restricted to patients who had undergone a 2nd line of therapy (platinum-based) (50 %)[4]. The additional uncertainties addressed in IQWiG's dossier assessment regarding the remaining derivation steps still exist. It is assumed that these are largely absorbed through the specification of a range.

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 Zejula (active ingredient: niraparib) at the following publicly accessible link (last access: 15 May 2021):
https://www.ema.europa.eu/documents/product-information/zejula-epar-product-information_de.pdf

Treatment with niraparib should only be initiated and monitored by specialists in internal medicine, haematology and oncology, specialists in gynaecology and obstetrics and others, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with ovarian cancer.

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 June 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number

3 Buttmann-Schweiger N, Kraywinkel K. Epidemiology of ovarian cancer in Germany. The Oncologist 2019; 25(2): 9298
4 Kantar Health. TREATMENT ARCHITECTURE: Western Europe Ovarian Cancer. 2017.

of treatments/patients/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patients/year	Treatment duration/ treatment (days)	Days of treatment/ patients/ year
Medicinal product to be assessed				
Niraparib	continuously, once a day	365	1	365
Appropriate comparator therapy				
Olaparib	continuously, twice a day	365	1	365
Monitoring wait-and-see approach	incalculable			

Consumption:

Designation of the therapy	Dosage/ Application	Dosage/ patients/ days of treatment	Usage by potency/ day of treatment	Treatment days/ Patients/ year	Average annual consumption by potency
Medicinal product to be assessed					
Niraparib	300 mg	300 mg	3 x 100 mg	365	1,095 x 100 mg
Appropriate comparator therapy					
Olaparib (FCT)	300 mg	600 mg	4 x 150 mg	365	1,460 x 150 mg
Olaparib (HC)[5]	400 mg	800 mg	16 x 50 mg	365	5,840 x 50 mg

[5] Only for the subpopulation of patients with a platinum-sensitive relapse of BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who respond (complete or partial response) to platinum-based chemotherapy.

Designation of the therapy	Dosage/ Application	Dosage/ patients/ days of treatment	Usage by potency/ day of treatment	Treatment days/ Patients/ year	Average annual consumption by potency
Monitoring wait-and-see approach	incalculable				
Abbreviations: HC = hard capsules; FCT = film-coated tablets					

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. I To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Niraparib	84	€ 6,628.48	€ 1.77	€ 377.97	€ 6,248.74
Appropriate comparator therapy					
Olaparib (FCT)	112	€ 5,616.98	€ 1.77	€ 317.51	€ 5,297.70
Olaparib (HC)3	448	€ 5,616.98	€ 1.77	€ 317.51	€ 5,297.70
Monitoring wait-and-see approach	incalculable				
Abbreviations: HC = hard capsules; FCT = film-coated tablets					

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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 standard 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 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 11 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of niraparib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 6 VerfO.

By letter dated 02 February 2021 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 niraparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 May 2021. The deadline for submitting written statements was 25 May 2021.

The oral hearing was held on 7 June 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the 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 July 2021, and proposed resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 August 2020	Determination of the appropriate comparator therapy
Working group Section 35a	1 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2021	Conduct of the oral hearing
Working group Section 35a	15 June 2021 29 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 July 2021	Concluding discussion of the draft resolution
Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Berlin, 15 July 2021

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

Prof. Hecken