Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Niraparib (Reassessment of an Orphan Drug after the € 50 Million Turnover Limit Was Exceeded (Ovarian Carcinoma, Tubal Carcinoma, or Primary Peritoneal Carcinomatosis; Maintenance Treatment after Second-Line Therapy))

of 2 April 2020

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 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 epithelial 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 of the Council of 16 December 1999.

At its session on 7 June 2018, the G-BA passed a resolution 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 SGB V.

If the turnover of the orphan drugs with statutory health insurance at pharmacy sales prices as well as outside statutory medical care, including value added tax, exceeds € 50 million in the last twelve calendar months, the pharmaceutical company must, within three months of being requested to do so by the Federal Joint Committee, submit evidence in accordance with Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

The pharmaceutical company was informed about the exceeding of the € 50 million turnover limit by letter dated 27 June 2019 and was requested to submit a dossier for the benefit assessment in accordance with 35a SGB V. The pharmaceutical company submitted the final dossier to the G-BA in due time 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.

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 15 January 2020, 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 niraparib 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 niraparib.

In the light of the above and taking into account the statements 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 niraparib (Zejula®) in accordance with the product information

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.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for niraparib as monotherapy was determined as follows:

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; maintenance treatment

- 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

[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.

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, olaparib, paclitaxel, rucaparib, topotecan, trabectedin, and treosulfan are available in addition to niraparib.

On 2. No non-medicinal treatments are considered.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies 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. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies.

For the present therapeutic indication, 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 six and twelve months after completion of platinum-containing chemotherapy.

According to 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 niraparib, which is currently under evaluation, the PARP inhibitors olaparib and rucaparib also have corresponding marketing authorisation. Niraparib is approved as a medicinal product for the treatment of a rare disease (orphan drugs).

The PARP inhibitor olaparib was first approved on 16 December 2014 for maintenance treatment in adult patients with platinum-sensitive relapses of BRCA-mutated (germline and/or somatic) *high-grade* serous epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma responding 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.

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

According to the current German S3 guideline, published in January 2019, patients with relapse of high-grade ovarian cancer should be offered maintenance treatment with a PARP inhibitor after response to platinum-containing recurrence therapy (recommendation level B). In the body text of the guideline, 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.

In addition, bevacizumab is approved 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 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 as an appropriate comparator therapy.

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

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

2.1.3 Extent and probability of the additional benefit

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

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; maintenance treatment, an additional benefit is not proven.

Justification:

In the absence of a direct comparative study to prove an additional benefit of niraparib compared with olaparib, the pharmaceutical company submitted an adjusted indirect comparison in the dossier. For this purpose, the NOVO RCT is on the niraparib side and the two SOLO2 RCTs and Study 19 on the olaparib side with placebo as the bridge comparator.

NOVA study

The NOVA study is a multi-centre, randomised, double-blind, controlled Phase III study comparing niraparib with placebo in two independent cohorts. Adult patients with a platinum-sensitive relapse of ovarian cancer who had responded fully or partially to previous platinum-containing chemotherapy were enrolled in the study 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. For enrolment, patients also should have had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1.

A total of 553 patients were enrolled in the NOVA study. 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). The patients were randomised at a ratio of 2:1 and assigned to treatment with niraparib (N = 372 (gBRCAmut: 138; non-gBRCAmut: 234)) or placebo (N = 181 (gBRCAmut: 65; non-gBRCAmut: 116)). The patients were stratified according to the time to disease progression after last dose of penultimate platinum chemotherapy before enrolment (6 to 12 months vs > 12 months), the response (complete or partial) during the last platinum containing chemotherapy, and the use of bevacizumab in connection with the penultimate or last platinum containing therapy regime (yes vs no).

Treatment with the study medication was continued until disease progression or discontinuation for other reasons (e.g. because of AE or patient decision). However, patients were also able to continue treatment despite disease progression if the investigator considered that the patients had a clinical benefit. A change of patients from the control arm to the intervention arm was not planned in the NOVA study.

NOVA is conducted in 128 study centres in Asia, Europe, and North America. The currently ongoing study started in August 2013.

For the NOVA study, an a priori planned data cut-off of 30 May 2016 is currently available for primary analysis. For this data cut-off, data are available for all patient-relevant outcomes. This data cut-off is used for the present benefit assessment.

Study 19

Study 19 is a multi-centre, double-blind, randomised controlled trial comparing olaparib with placebo. The study was conducted from August 2008 to May 2016 and has thus already been completed. The study included adult patients with a platinum-sensitive relapse of high-grade serous ovarian cancer who had responded fully or partially to previous platinum-containing chemotherapy. In Study 19, patients were enrolled regardless of their BRCA mutation status. However, this was determined after to the primary data cut-off. Before the start of study, patients should have had a performance status of 0 or 2. according to ECOG-PS.

The 265 patients enrolled were randomised the olaparib arm (N = 136) and the placebo arm (N = 129) at a ratio of 1:1. The patients were stratified according to the time to disease progression after last dose of penultimate platinum chemotherapy before enrolment (6 to 12 months vs > 12 months), the objective response (complete or partial) to the last platinum containing chemotherapy before study inclusion, and Jewish descent (yes vs no; because of an increased BRCA mutation prevalence in this population).

Treatment with the study medication was continued until disease progression, discontinuation because of AE, or withdrawal of consent. However, patients were also able to continue treatment despite disease progression if the investigator considered that the

patients had a clinical benefit. A change of patients from the control arm to the intervention arm was not allowed in Study 19. Because olaparib was already available in some study centres at the time of the study, some patients from the placebo arm were received olaparib as follow-up therapy.

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

For Study 19, data are available for the 6th or last data cut-off of 9 May 2016 for all patient-relevant outcomes except health-related quality of life. Data on health-related quality of life are available only from the 1st data cut-off because their survey was discontinued. For the present benefit assessment, the 6th data cut-off is used.

SOLO2 study

The SOLO2 study is a multi-centre, double-blind, randomised controlled trial comparing olaparib with placebo. The ongoing global study, which started in August 2013, included adult patients with a platinum-sensitive relapse of high-grade serous ovarian cancer who had responded fully or partially to previous platinum-containing chemotherapy. Only patients with BRCA mutation were enrolled in the SOLO2 study. For enrolment, patients should have had a performance status of 0 or 1. according to ECOG-PS.

The 295 patients enrolled were randomised the olaparib arm (N = 196) and the placebo arm (N = 99) at a ratio of 2:1. Patients were stratified according to the response (complete or partial) to the last platinum containing chemotherapy and the time to disease progression after last dose of penultimate platinum chemotherapy before enrolment (6 to 12 months vs > 12 months).

In China, there was a cohort with the same study protocol that was started later and thus separately investigated. This cohort is not considered in the present benefit assessment because no relevant additional information is expected from it.

Treatment with the study medication was continued until disease progression, discontinuation because of AE, or withdrawal of consent. However, patients were also able to continue treatment despite disease progression if the investigator considered that the patients had a clinical benefit. A change of patients from the control arm to the intervention arm was not allowed in the SOLO2 study. Because olaparib was already available in some study centres at the time of the study, some patients from the placebo arm were received olaparib as follow-up therapy.

SOLO2 is conducted in 119 study centres in Asia, Australia, Europe, and North and South America.

For the SOLO2 study, an a priori planned data cut-off of 19 September 2016 is currently available for primary analysis. For this data cut-off, data are available for all patient-relevant outcomes. This data cut-off is used for the present benefit assessment.

On the indirect comparison

The adjusted indirect comparison presented by the pharmaceutical company in the dossier was performed separately for three sub-populations. These 3 sub-populations represented patients with a BRCA germline mutation (gBRCA), patients with BRCA mutations of any kind (BRCAm), and patients without BRCA mutations (BRCAwt).
The NOVA and SOLO2 studies were used for the sub-population of patients with BRCA germline mutations (gBRCA) and the NOVA study and Study 19 for the sub-population of patients with all types of BRCA mutations (BRCAm) and patients without BRCA mutations (BRCAwt).

In the dossier evaluation of the IQWiG, the approach of the pharmaceutical company was not considered appropriate for the following reasons. On one hand, the patients with BRCA germline mutation from the NOVA study were included in the analysis twice according to the

procedure of the pharmaceutical company. The subgroups submitted by the pharmaceutical company are thereby not disjunctive. Furthermore, neither the approved therapeutic indication of niraparib nor the appropriate comparator therapy for niraparib as defined by the G-BA differentiate according to the BRCA mutation status. Furthermore, against the background of the high risk of bias for all relevant endpoints, only a meta-analytical consideration of the SOLO2 study and Study 19 provides sufficient certainty of results for an indirect comparison.

For Study 19, a high risk of bias across endpoints results from the high proportion of patients in both treatment arms with incorrect classification in the stratified block randomisation. This results in a high risk of bias for all endpoints. Other endpoint specific reasons are added. For the SOLO2 study, there is a low risk of bias across endpoints. However, because of endpoint-specific reasons, there is also a high risk of bias for some endpoints.

Against this background, IQWiG calculated an adjusted indirect comparison in its dossier evaluation. This took into account the respective total populations of the studies themselves. For this indirect comparison according to Bucher, the NOVA study formed the side of the intervention (niraparib) compared with the bridge comparator placebo. For the indirect comparison, the SOLO2 study and Study 19 formed the side of the appropriate comparator therapy (olaparib) compared with the bridge comparator placebo. In this context, the SOLO2 study and Study 19 were considered in the context of a meta-analytical summary, which was taken from the previous benefit assessment of olaparib (resolution of 6 December 2018).

Because there were no major differences between the NOVA and SOLO2 studies and Study 19 in terms of the patient populations included and the study design, the studies are generally considered sufficiently similar for an adjusted indirect comparison.

The generally accepted state of medical knowledge as well as the written comments on the present benefit assessment showed that in the present indication, the BRCA mutation status in clinical practice is not to be regarded as decisive with regard to therapy decisions. A subdivision according to BRCA mutation status can thus be regarded as dispensable. Against the background of the reasons given by IQWiG and the written statements of the clinical experts, the G-BA considers it appropriate to use the adjusted indirect comparison for the present benefit assessment, taking into account the total population of the studies and under meta-analytical summary of the SOLO2 study and Study 19.

Extent and probability of the additional benefit

In the NOVA and SOLO2 studies as well as Study 19, overall survival was defined as the period from randomisation to death by any cause.

For the endpoint overall survival, the adjusted indirect comparison did not show a statistically significant difference between niraparib and olaparib (HR: 0.99 [95% CI: 0.61; 1.60]; p = 0.956). In the NOVA study, median survival was not yet achieved because of the low number of events; final analyses on the overall survival endpoint are pending.

No additional benefit is identified for the overall survival endpoint.

Morbidity

Progression-free survival (PFS)

In the NOVA and SOLO2 studies as well as Study 19, progression-free survival was defined as the time between randomisation and the time of disease progression or death.

Because no results on progression-free survival were reported for the total study population, no usable data are available for this endpoint.

Health status (EQ-5D visual analogue scale)

In the NOVA and SOLO2 studies, the general health status was assessed using the visual analogue scale of EQ-5D.

In the NOVA study, the survey was conducted up to 8 weeks after disease progression. In the SOLO2 study, all patients were followed up for 24 months or until the data cut-off of the primary analysis. Thus, in the SOLO2 study, the survey was also conducted beyond disease progression.

Against this background, there are considerable differences in the follow-up strategy of the two studies with regard to the health status endpoint. The analyses between the NOVA and SOLO2 studies are thus not comparable and cannot be used for the indirect comparison. There is therefore no usable data for the endpoint health status.

Symptomatology

In the NOVA study, symptomatology was assessed using the FOSI-8 symptom score, which consists of 8 items that are part of the overall FACT-O questionnaire. On the olaparib side, evaluations of the FOSI-8 are only available from Study 19.
Because 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 at the study level against the background of the high risk of bias of Study 19.
There are therefore no usable data available with respect to symptomatology.

Quality of life

In the SOLO2 study and Study 19, the disease-specific questionnaire FACT-O was used to survey the health-related quality of life. However, in the NOVA study, there was no survey of the total score of FACT-O. Therefore, no sufficient data are available for an indirect comparison.
There are therefore no usable data on health-related quality of life.

Side effects

In the NOVA study, a survey of adverse events (AE) and severe AE (CTCAE grade ≥ 3) was planned until the last administration of the study medication. Serious adverse events should be followed up until 30 days after the last administration of the study medication.
In study 19, follow-up of all endpoints in the side effects category was planned until 30 days after the last dose of the study medication.
For the SOLO2 study, follow-up of AE and severe AE was planned until 30 days after the last dose of the study medication; specific AE were to be observed indefinitely beyond the end of treatment.

Based on the information on adverse events in the NOVA study in the dossier of the pharmaceutical company, the IQWiG was unable to initially calculate an adjusted indirect comparison because of the insufficient certainty of results in the NOVA study. This was particularly due to the fact that the data on patients at risk in the Kaplan-Meier curves of the event time analyses were discrepant to the median observation times in the study arms. Against this background, it was not possible to use the Kaplan-Meier curves for evaluation (e.g. to assess the certainty of results for individual endpoints).
Within the framework of the written statement procedure on the present benefit assessment, the pharmaceutical company explained that the discrepancies resulted from the application of a faulty censoring mechanism for the respective analyses. The pharmaceutical company submitted correspondingly corrected analyses with the written statement; in these, the patients were censored at the actual end of observation. The pharmaceutical company did not provide the data for the NOVA study for the entire study population but rather separate

evaluations for the sub-population of patients with BRCA germline mutation (gBRCAmut) and patients without BRCA germline mutation or patients with BRCA mutation and BRCA wild type of their ovarian carcinoma (non-gBRCAmut).
Because IQWiG considered it appropriate to use the total population of the NOVA study for the benefit assessment of niraparib for the reasons listed above, the analyses were also meta-analytically summarised by IQWiG in its addendum to the benefit assessment, and an adjusted indirect comparison was calculated. This procedure is followed by the G-BA.

On the niraparib side of the indirect comparison, there are only data from one study (NOVA study), the results of which are potentially biased for the endpoints SAE and severe AE (CTCAE grade ≥ 3) in relation to specific endpoints. Thus, for these endpoints, there is sufficient certainty of results for deriving an additional benefit from the indirect comparison only if there are sufficiently large effects that cannot be called into question by potential distortions alone.
The latter also applies to the endpoint discontinuation because of AE because for this endpoint, there is limited certainty of results in all three studies. This results in particular from the fact that after discontinuation of therapy for reasons other than AE (which is a competing event for discontinuation because of UE), AE that would have led to discontinuation may occur. However, for these, the discontinuation criterion can no longer be recorded. The proportion of such AE cannot be estimated.

Adverse events (AE)

On the niraparib side of the indirect comparison, in the NOVA study in the intervention arm, an adverse event occurred in 100% of the patients; in the comparison arm, in 95.5% of the patients.
On the olaparib side of the indirect comparison, in Study 19 or the SOLO2 study in the intervention arm, an adverse event occurred in 97.1% or 98.5% of the patients; in the comparison arm, in 94.9% of the patients.

Serious adverse events (SAE)

The results for the endpoint SAE do not indicate a statistically significant difference between niraparib and olaparib (HR: 1.14 [95% CI: 0.57; 2.30]). However, for a reliable interpretation of this result, as explained above, there is insufficient certainty of results for this data constellation.

Severe AE (CTCAE grade ≥ 3)

The adjusted indirect comparison shows a statistically significant effect for the endpoint severe AE to the disadvantage of niraparib compared with olaparib. Because of the magnitude of this effect, there is a sufficiently high qualitative certainty of results for its interpretation. Because of non-usable data for an indirect comparison of the specific AE (here: CTCAE grade ≥ 3), it is not possible to evaluate in detail which side effects are responsible for the disadvantage in severe AE. For both active ingredients, cytopenias are the most frequent AE in CTCAE grade ≥ 3.

Discontinuation because of AE

The results for the endpoint discontinuation because of AE do not indicate a statistically significant difference between niraparib and olaparib (HR: 2.15 [95% CI: 0.46; 9.97]). However, also for this endpoint, for a reliable interpretation of this result, as explained above, there is insufficient certainty of results for this data constellation.

Specific AE

A selection of specific AE based on frequencies and differences between treatment arms was not possible because of the lack of evaluations for the total population of the NOVA study. For selected AE of particular significance (acute myeloid leukaemia, myelodysplastic syndrome, pneumonitis), the calculation of an adjusted indirect comparison was not meaningful because against the background of the very few events, it was not possible to produce a sufficiently large treatment effect.
There is no thus no usable data for the specific AE.

Overall assessment

To assess the additional benefit of niraparib compared with olaparib, an adjusted indirect comparison of niraparib (NOVA study) with olaparib (SOLO2 study and Study 19) via the bridge comparator placebo is available. The adjusted indirect comparison yields results on mortality (overall survival) and side effects.

In the endpoint category mortality, the indirect comparison for the overall survival endpoint did not show a statistically significant difference between niraparib and olaparib. Only a small number of events have occurred on the niraparib side (NOVA study) at the time of this data cut-off. Final analyses from the NOVA study on the overall survival endpoint are pending. No additional benefit is identified for the overall survival endpoint.

No usable data are available for the endpoint category morbidity because there were considerable differences in the follow-up strategy between the NOVA and SOLO2 studies with regard to the endpoint health status. The corresponding analyses were therefore not comparable. Furthermore, it was not possible to use the data on symptomatology (surveyed using FOSI-8) because data from a study with sufficient certainty of results were not available on each side of the indirect comparison.

For the endpoint category of health-related quality of life, there are also no usable data because the NOVA study did not survey health-related quality of life.

In the side effects category, the indirect comparison for the endpoint severe AE (CTCAE grade ≥ 3) shows a disadvantage of niraparib compared with olaparib. Because of non-usable data for an indirect comparison of the specific AE (here: CTCAE grade ≥ 3), it is not possible to evaluate in detail which side effects are responsible for the disadvantage in severe AE. For both active ingredients, cytopenias are the most frequent AE in CTCAE grade ≥ 3.
The results for the endpoints SAE and discontinuation because of AE do not indicate a statistically significant difference between niraparib and olaparib. However, for a reliable interpretation of the results for these endpoints, there is no sufficient certainty of results for the existing data constellation.
No usable data are available for the specific AE, in particular because of the lack of evaluations for the total population of the NOVA study.

For overall survival, the NOVA study showed no difference between niraparib and olaparib, although event numbers were still low.

Taking into account the clinical relevance, the disadvantage in side effects in the existing data constellation does not reach a level that would justify a lower benefit in the overall assessment given that moderate disadvantages were shown only for the endpoint severe AE (CTCAE grade ≥ 3).

In the overall view, the G-BA concludes that an additional benefit of niraparib compared with olaparib 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 niraparib 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 the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

For this assessment, the overall survival data from the NOVA study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending.

In view of the fact that clinical data on overall survival relevant for the benefit assessment of the medicinal product are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the additional benefit of niraparib is available. The limitation allows the expected final results from the NOVA study to be included in the benefit assessment of the medicinal product according to Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 1 October 2020 to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the dossier should include the results expected in second quarter of 2020 from the final analysis on overall survival as well as all other patient-relevant outcomes from the NOVA study used to demonstrate an additional benefit. In particular for the specific adverse events, the data for the total population of the study should also be provided.

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, number 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product niraparib 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 proving an additional benefit of niraparib in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for the medicinal product niraparib can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 – 4 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the renewed benefit assessment of the active ingredient niraparib because the € 50 million turnover limit was exceeded. Niraparib is approved 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.

Niraparib has received marketing authorisation as an orphan drug.

Olaparib or “a monitoring wait-and-see approach” was determined as an appropriate comparator therapy by the G-BA:

To prove an additional benefit of niraparib compared with olaparib, the pharmaceutical company submits an adjusted indirect comparison via the bridge comparator placebo. The randomised, double-blind, controlled NOVA study (niraparib vs. placebo) was presented for the niraparib side, and the randomised, double-blind, controlled studies SOLO2 and Study 19 (olaparib vs placebo) for the olaparib side.
The approach of the pharmaceutical company to present the results differentiated according to the BRCA mutation status of the patients was not followed in the present assessment. Instead, for the adjusted indirect comparison, the total populations of the studies were considered under meta-analytical summary of the SOLO2 study and Study 19.

In the endpoint category mortality, the indirect comparison did not show a statistically significant difference between niraparib and olaparib for the overall survival endpoint. Only a small number of events occurred on the niraparib side (NOVA study) at the time of this data cut-off. Final analyses from the NOVA study on the overall survival endpoint are pending.

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

In the side effects category, the indirect comparison for the endpoint severe AE (CTCAE grade ≥ 3) showed a disadvantage of niraparib compared with olaparib.
The results for the endpoints SAE and discontinuation because of AE did not indicate a statistically significant difference between niraparib and olaparib; however, there was insufficient certainty of results in this respect. No usable data were available for the specific AE.

For overall survival, the NOVA study showed no difference between niraparib and olaparib, although event numbers were still low.

Taking into account the clinical relevance, the disadvantage in side effects in the existing data constellation does not reach a level that would justify a lower benefit in the overall assessment given that moderate disadvantages were shown only for the endpoint severe AE (CTCAE grade ≥ 3).

In the overall view, the G-BA concludes that an additional benefit of niraparib compared with olaparib 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).

The IQWiG estimates that the derivation of patient numbers by the pharmaceutical company is largely comprehensible but is subject to uncertainty because of uncertainties regarding the methodological procedure.

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 assessments of olaparib (resolution of 6 December 2018) and rucaparib (resolution of 15 August 2019).

These are afflicted with uncertainties because 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 of the IQWiG in the relevant benefit assessment

procedure for niraparib supports the figures of the pharmaceutical company in their order of magnitude assuming an average survival time of 2–3 years in the present therapeutic indication.

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: 28 January 2020):
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 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 March 2020).

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 of treatments/patient/year”, the 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/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Niraparib	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Olaparib	continuously, 2 × daily	365	1	365
Monitoring wait-	not quantifiable			

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
and-see approach				

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Niraparib	300 mg	300 mg	3 × 100 mg	365	1,095 × 100 mg
Appropriate comparator therapy					
Olaparib (FCT)	300 mg	600 mg	4 × 150 mg	365	1,460 × 150 mg
Olaparib (HC)[2]	400 mg	800 mg	16 × 50 mg	365	5,840 × 50 mg
Monitoring wait-and-see approach	not quantifiable				

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 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 costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Niraparib	84 HC	€ 8,214.71	€ 1.77	€ 468.56	€ 7,744.38
Appropriate comparator therapy					
Olaparib 150 mg	112 FCT	€ 6,730.14	€ 1.77	€ 381.08	€ 6,347.29
Olaparib 50 mg	448 HC	€ 6,730.14	€ 1.77	€ 381.08	€ 6,347.29
Monitoring wait-and-see approach	not quantifiable				
Abbreviations: HC = hard capsules; FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be 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

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 23 July 2019.

On 15 October 2019, 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 6 VerfO.

By letter dated 15 October 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 niraparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 January 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 January 2020. The deadline for submitting written statements was 5 February 2020.

The oral hearing was held on 24 February 2020.

By letter dated 24 February 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 March 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	23 July 2019	Determination of the appropriate comparator therapy
Working group Section 35a	19 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 February 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 March 2020 18 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure

Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken