Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Rucaparib (after at least 2 previous therapies, with BRCA mutations)

of 15 August 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient rucaparib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 March 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 1 VerfO on 26 February 2019.

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

The G-BA came to a resolution on whether an additional benefit of rucaparib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in

Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of rucaparib.

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of rucaparib (Rubraca®) in accordance with product information

Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), *high-grade* epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy

Monotherapy with topotecan *or* monotherapy with pegylated liposomal doxorubicin (PLD)

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

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

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

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

[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.

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

On 1. In accordance with the authorisation status, cyclophosphamide, doxorubicin, liposomal doxorubicin (PLD), epirubicin, etoposide, melphalan, topotecan, trabedectin (in combination with pegylated liposomal doxorubicin), and treosulfan may be considered.

On 2. No non-medicinal treatments are considered in this therapeutic indication.

On 3. No resolutions have been passed for this therapeutic indication.

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

Guidelines consistently recommend that patients with platinum-sensitive relapse of ovarian cancer should be treated with further platinum-containing chemotherapy. However, because the present therapeutic indication of rucaparib only covers patients who do not tolerate further platinum-containing chemotherapy, re-therapy with carboplatin is not considered.

For patients for whom further platinum-based treatment is not an option, the guidelines primarily recommend monochemotherapy. On the other hand, combination therapies are critically discussed because of increased toxicity. In particular, there is evidence for monotherapy with the active ingredients paclitaxel, topotecan, gemcitabine, or pegylated liposomal doxorubicin (PLD).

However, gemcitabine is only approved in combination with carboplatin to treat patients with platinum-sensitive relapses. The marketing authorisation of paclitaxel covers only patients in the second line. Because of the lack of marketing authorisation in this therapeutic indication, the active ingredients gemcitabine and paclitaxel are not suitable as appropriate comparator therapies.

Another treatment option for platinum-sensitive patients listed in the guidelines is therapy with trabectedin in combination with pegylated liposomal doxorubicin (PLD). However, in the pivotal OVA-301 study investigating the efficacy of trabectedin in combination with PLD, combination therapy shows only one overall survival benefit for partially sensitive patients. However, this sub-population does not cover the whole therapeutic indication of rucaparib. For the total population of the OVA-301 study, neither an advantage in overall survival nor an advantage in quality of life could be shown.

Furthermore, it cannot be deduced that monotherapy with topotecan is to be preferred to monotherapy with pegylated liposomal doxorubicin (PLD).

As a result, the G-BA has therefore determined monotherapy with topotecan or monotherapy with pegylated liposomal doxorubicin (PLD) as appropriate comparator therapy for rucaparib in the present therapeutic indication.

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 rucaparib is assessed as follows:

An additional benefit is not proven.

Justification:

To demonstrate the additional benefit, the pharmaceutical company used data from the uncontrolled rucaparib studies ARIEL2 and Study 10 (CO-338-010) as well as from two studies on appropriate comparator therapy (Gordon 2001 and Kaye 2012). In a descriptive comparison, the pharmaceutical company compares the results of an integrated efficacy analysis based on parts of the studies ARIEL2 and study 10 with the results of the studies Gordon 2001 and Kaye 2012.

However, it is not possible to evaluate the additional benefit based on this data basis. On one hand, the patients included in the studies ARIEL2 and Study 10 do not sufficiently correspond to the therapeutic indication to be evaluated. This also applies to the studies on the appropriate comparator therapy. Furthermore, in accordance with the inclusion criteria, no sufficient similarity can be found between the patient populations of the rucaparib studies and the studies on appropriate comparator therapy. In addition, only data on patient-relevant endpoints for individual frequent adverse events are available from the descriptive comparison.

The additional benefit for rucaparib to treat adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy is thus not proven.

2.1.4 Summary of the assessment

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

Rubraca has been given a conditional marketing authorisation.

The therapeutic indication assessed here is as follows:

Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

The G-BA has determined a monotherapy with topotecan or a monotherapy with pegylated liposomal doxorubicin (PLD) as appropriate comparator therapy.

To demonstrate the additional benefit, the pharmaceutical company presented a descriptive comparison between an efficacy analysis based on the rucaparib studies ARIEL2 and Study 10 as well as data from two studies on appropriate comparator therapy.

The additional benefit cannot be assessed based on the evidence provided. Thus, an additional benefit 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 resolution will be based on the information from the dossier of the pharmaceutical company regarding the number of patients. The procedure of the pharmaceutical company is mathematically plausible. However, overall there are uncertainties and ambiguities because of methodological shortcomings and a weak data basis.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Rubraca® (active ingredient: rucaparib) at the following publicly accessible link (last access: 5 July 2019):

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

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

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

2.4 Treatment costs

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Rucaparib	continuous, 2 × daily	365	1	365
Appropriate comparator therapy				
Topotecan	on day 1–5 followed by at least a 16-day treatment break	17	5	85
Pegylated	1 x every 4	13	1	13

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
liposomal doxorubicin (PLD)	weeks			

Usage and consumption:

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

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[2].

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Rucaparib	600 mg	1200 mg	4 × 300 mg	365	1460 × 300 mg
Appropriate comparator therapy					
Topotecan	1.5 mg/m² BSA	2.85 mg	1 x 3 mg/3 ml	85	85 × 3 mg
Pegylated liposomal doxorubicin (PLD)	50 mg/m² BSA	95 mg	2 x 50 mg/25 ml	13	26 × 50 mg

Costs:

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Rucaparib	60 FCT	€ 4,647.57	€ 1.77	€ 262.15	€ 4,383.65
Appropriate comparator therapy					
Topotecan	1 IFK	€ 236.13	€ 1.77	€ 10.68	€ 223.68
Pegylated liposomal doxorubicin (PLD)	1 IFK	€ 1877.59	€ 1.77	€ 103.96	€ 1771.86
Abbreviations: FCT = film-coated tablets, IFK = concentrate for the preparation of an infusion solution					

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

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the usual expenditure in the course of the treatment are not shown.

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

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

On 26 February 2019, the pharmaceutical company submitted a dossier for the benefit assessment of rucaparib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 26 February 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient XYZ.

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

The oral hearing was held on 9 July 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 August 2019, and the proposed resolution was approved.

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

Chronological course of consultation

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

Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

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

Prof Hecken