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 Encorafenib (New Therapeutic Indication: Metastatic Colorectal Cancer with a BRAF V600E Mutation after Prior Systemic Therapy, in Combination with Cetuximab)

of 17 December 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 based on 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 encorafenib (Braftovi) was listed for the first time on 15 October 2018 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 2 June 2020, encorafenib received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).
On 30 June 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient atezolizumab with the new therapeutic indication “Encorafenib is indicated: […] in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy” in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 October 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 encorafenib compared with the appropriate comparator therapy could be determined based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit based on their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of encorafenib.

In the light of the above and taking into account the written 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

2.2 Approved therapeutic indication of encorafenib (Braftovi) in accordance with the product information

Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

Therapeutic indication of the resolution (resolution of 17 December 2020):

See therapeutic indication according to marketing authorisation

2.3 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy

Appropriate comparator therapy for encorafenib in combination with cetuximab:

- A patient-individual therapy with the selection of
  - 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab
  - Capecitabine + oxaliplatin ± bevacizumab
  - 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab
  - Irinotecan ± cetuximab or panitumumab
  - Trifluridine/tipiracil
  - 5-fluorouracil ± bevacizumab
  - Capecitabine ± bevacizumab

[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.

- taking into consideration the general condition and the type and number of previous therapies.

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 applications 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.

No active ingredients are explicitly approved for the specific treatment situation of patients with metastatic colorectal cancer with a BRAF V600E mutation who have received prior systemic therapy. For the treatment of metastatic colorectal carcinoma, which also includes BRAF V600E mutations, after prior systemic therapy, the active ingredients trifluridine/tipiracil, 5-fluorouracil (possibly in combination with calcium folinate), capecitabine, oxaliplatin, irinotecan, mitomycin, regorafenib, bevacizumab, ramucirumab, aflibercept, cetuximab, and panitumumab are available as monotherapy or as part of combination therapies.

On 2.

For the therapeutic indication, a non-medicinal treatment cannot be considered.

On 3.

For the therapeutic indication of metastatic colorectal carcinoma, the following resolutions or guidelines of the G-BA exist for medicinal applications:

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

- Resolution of 1 October 2020: Trifluridine/tipiracil
- Resolution of 1 September 2016: Ramucirumab
- Resolution of 17 March 2016: Regorafenib
- Resolution of 15 August 2013: Aflibercept

On 4.

The general state of medical knowledge on which the findings of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

The evidence available specifically on patients with BRAF V600E-mutated tumours who have received at least one prior systemic therapy is limited overall. The systematic reviews and Cochrane reviews do not address the specific patient population of BRAF V600 mutated patients. In the guidelines, the therapy recommendations for BRAF V600 mutated patients are predominantly based on the first-line situation. However, the present therapeutic indication addresses second-line therapy and subsequent lines of therapy.

Because of the poor prognosis for patients with a BRAF V600 mutation, some guidelines recommend early initiation of intensified chemotherapy (e.g. with FOLFOXIRI ± bevacizumab). However, in the guidelines, the evidence for this recommendation is considered to be merely hypothesis-generating because it involves only small sub-group analyses. Alternatively, inclusion in a clinical study is also recommended.

With regard to subsequent lines of therapy, guidelines mention, amongst others, the use of a chemotherapy doublet in combination with VEGF inhibitors as well as experimental procedures.

Overall, however, the evidence available and the corresponding statements in guidelines for patients with BRAF V600E-mutated tumours show that a specific standard therapy for these patients after prior systemic therapy cannot be named. According to the written statement of the Scientific Medical Societies in the benefit assessment procedure, a BRAF mutation is currently used as a prognostic marker but not as a predictive marker.

Thus, in principle, those therapy options are considered as appropriate comparator therapy that represent a standard regardless of BRAF mutation status. For the overall population of patients with metastatic colorectal cancer (i.e. irrespective of BRAF V600E mutation status) the guidelines for the second line mention various combination or monotherapies, selecting the active ingredients 5-fluorouracil (possibly in combination with calcium folinate), capecitabine, oxaliplatin and/or irinotecan, and VEGF or EGFR inhibitors. Second-line treatment in the context of sequential use of active ingredients should be based on the previous therapy. To date, the superiority of a particular sequence has not been demonstrated for the overall population of patients with metastatic colorectal cancer. In the guidelines, for patients who have received an oxaliplatin-containing therapy regime in the first line, an irinotecan-containing chemotherapy is mentioned by default for the following therapy line and vice versa. Specifically for second-line therapy, evidence is available for the combination therapies 5-fluorouracil, folinic acid, and oxaliplatin (FOLFOX), 5-fluorouracil, folinic acid and irinotecan (FOLFIRI), or capecitabine and oxaliplatin (CAPOX). If the general condition is reduced, monotherapies (5-fluorouracil/folinic acid or capecitabine) can be used in combination with bevacizumab. The use of irinotecan-containing monotherapy is mentioned in the guidelines as part of sequential chemotherapy after fluorourpyrimidine monotherapy.

In addition, with aflibercept and ramucirumab, two further anti-VEGF therapeutics that are approved in the present therapeutic indication and can be used after prior oxaliplatin-containing chemotherapy. Within the framework of the benefit assessment according to Section 35a SGB V, an indication of a minor additional benefit was found for aflibercept in combination with FOLFIRI compared with FOLFIRI (resolution of 15 August 2013), while an additional benefit for ramucirumab in combination with FOLFIRI compared with FOLFIRI is not proven (resolution 1 September 2016). In several studies, the use of VEGF inhibitors (bevacizumab, aflibercept or ramucirumab) in combination with chemotherapy in the second line resulted in a significant prolongation of overall survival compared with chemotherapy alone. The use of VEGF inhibitors in the second line should therefore be considered for the overall population of patients with metastatic colorectal cancer.

EGFR inhibitors (cetuximab, panitumumab) can also be used in combination with FOLFIRI or irinotecan for patients with RAS wild-type tumours. Simultaneous mutations of RAS and BRAF genes are very rare and are thus considered mutually exclusive. It is therefore assumed that

EGFR inhibitors for BRAF-mutated tumours may be indicated here in principle. However, the role of anti-EGFR substances, also in the presence of a BRAF mutation, has not been conclusively clarified and is the subject of controversial discussions in the guidelines. In their written statements on the present benefit assessment, the clinical experts stated that in the reality of care, in the second-line and follow-up lines, tumours with BRAF mutation are currently treated in the same way as tumours without BRAF mutation because of the lack of specific therapies and high-quality evidence. This also includes the use of EGFR inhibitors.

For the treatment of patients with metastatic colorectal carcinoma in later lines of therapy, two further therapy options are available: trifluridine/tipiracil and regorafenib. These are recommended in the guidelines for later lines of therapy. Within the framework of the benefit assessment according to Section 35a SGB V, a hint for a minor additional benefit was found for trifluridine/tipiracil compared with best supportive care (resolution of 1 October 2020).

Within the framework of the benefit assessment according to Section 35a SGB V, no additional benefit was proven for regorafenib compared with best supportive care (resolution of 17 March 2016). Regorafenib has been withdrawn from the market in Germany and is not available for standard care. Regorafenib is thus not considered an appropriate comparator therapy. Based on the evidence available, mitomycin is also not considered a suitable therapeutic option in the context of patient-individual therapy.

With regard to the aforementioned therapy options that can be considered for an appropriate comparator therapy in the present therapeutic indication, the specific therapy decision depends largely on individual patient factors, which usually include the general condition as well as the type and number of previous therapies.

Thus, a patient-individual therapy was determined as the appropriate comparator therapy, selecting the aforementioned therapy options and taking into consideration the general condition and the type and number of previous therapies.

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

Change of the appropriate comparator therapy:

The appropriate comparator therapy was originally determined as follows:

- A patient-individual therapy with the selection of
  - 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab
  - Capecitabine + oxaliplatin ± bevacizumab
  - 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab
  - Irinotecan
  - Trifluridine/tipiracil
  - 5-fluorouracil ± bevacizumab
  - Capecitabine ± bevacizumab
- taking into consideration the general condition and the type and number of previous therapies.

The addition of EGFR inhibitors (cetuximab, panitumumab) in combination with irinotecan-containing therapies to the appropriate comparator therapy takes into account in particular the written statements of the Scientific Medical Societies submitted in the present benefit assessment procedure.

This change in the appropriate comparator therapy means that the results of the BEACON CRC study presented by the pharmaceutical company in the dossier can be used for the

present assessment. In the dossier assessment of the IQWiG, these results were presented additionally. The results of the BEACON CRC study were also the subject of the written statements, which is why the change in the appropriate comparator therapy does not require the benefit assessment procedure to be carried out again.

2.4 Extent and probability of the additional benefit

In summary, the additional benefit of encorafenib in combination with cetuximab is assessed as follows:

For adult patients with metastatic colorectal cancer with a BRAF V600E mutation who have received at least one prior systemic therapy, there is a hint for a considerable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submits the results of the BEACON CRC pivotal study in the dossier. This study is used for the present benefit assessment.

BEACON CRC study

The BEACON CRC study is a 3-arm, open-label, international, randomised study comparing encorafenib + cetuximab and encorafenib + binimetinib + cetuximab in the intervention arms with cetuximab + irinotecan or cetuximab + FOLFIRI in the control arm. In the control arm of the BEACON CRC study, the investigator determined which of the two options was to be given in the event of allocation before randomisation. Because the marketing authorisation of encorafenib for the new therapeutic indication covers only encorafenib + cetuximab, the intervention arm encorafenib + binimetinib + cetuximab is not the subject of the present benefit assessment and is not described further below.

The BEACON CRC study included adult patients with metastatic colorectal cancer and a BRAF V600E mutated tumour who had tumour progression after 1 or 2 treatment regimens in the metastatic stage. Patients who had received 2 prior therapies had to have previously received or refused oxaliplatin unless it was contraindicated. Pre-treatment with RAF inhibitors, MEK inhibitors, or EGFR inhibitors was not allowed. A maximum Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 1 was allowed at the start of study. 220 patients were assigned to the intervention arm with encorafenib + cetuximab and 221 patients to the control arm.

The primary endpoint of the study was overall survival and overall response rate. Secondary endpoints were morbidity, health-related quality of life, and adverse events. The scheduled, primary data cut-off took place on 11 February 2019. The results of a further data cut-off of 15 August 2019 are used for the benefit assessment. This data cut-off was also submitted to the EMA. However, it is unclear whether this data cut-off was required by the EMA. The final analysis of the study is expected at the end of 2021.

Extent and probability of the additional benefit

Mortality

Overall survival

The BEACON CRC study showed a statistically significant prolongation of overall survival by treatment with encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab.

Taking into account the poor survival prognosis for patients with BRAF-mutated tumours and the advanced stage of disease and treatment, the extent of the prolongation achieved in overall survival is assessed as a significant improvement in therapeutic benefit.

Morbidity

Progression-free survival (PFS)

In the BEACON CRC study, PFS was collected as a secondary endpoint and is defined as the time from randomisation to the time of disease progression or death by any cause, whichever is earlier. The assessment of disease or tumour progression was carried out according to the RECIST criteria in Version 1.1. The primary analysis is based on tumour assessment by a blinded, independent review committee (BICR).

The result shows a statistically significant prolongation of PFS by treatment with encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint overall survival. The morbidity component “disease progression” was assessed solely by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria). Morbidity is thus not assessed primarily on the basis of disease symptoms but rather solely on the basis of asymptomatic, not directly patient-relevant findings.

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

In the BEACON CRC study, the symptomatology of the patients was assessed using the symptom scales of the EORTC QLQ-C30 questionnaire as well as the PGIC (Patient Global Impression of Change) questionnaire. The results obtained using PGIC were not used because the return rates were too low.

For the symptom scales of the EORTC QLQ-C30 questionnaire, the available responder analyses, operationalised as time to permanent deterioration, are not used because the data collection was discontinued significantly earlier and more frequently in patients in the control arm than in the intervention arm. The time to first deterioration in the control arm was potentially compared with the time to permanent deterioration in the intervention arm. Therefore, only the MMRM analyses with the standardised mean differences (Hedges’ g) are used by the G-BA. However, there are uncertainties because the endpoint surveys at the end of treatment and in the follow-up after 30 days were not included in the MMRM analyses.

The MMRM analyses on symptomatology show a relevantly lower burden of the symptom “diarrhoea” for patients treated with encorafenib + cetuximab. The symptoms of nausea and vomiting, loss of appetite, and constipation show statistically significant differences in the mean change. However, the 95% confidence intervals of the standardised mean difference (Hedges’ g) are not completely outside the irrelevance range of −0.2 to 0.2. Consequently, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

Health status

In the BEACON CRC study, health status was assessed using the EQ-5D VAS questionnaire. The present responder analyses, operationalised as time to permanent deterioration, are not used because drop-out occurred significantly more frequently and earlier in patients in the

control arm than in the intervention arm. The time to first deterioration in the control arm was potentially compared with the time to permanent deterioration in the intervention arm. Therefore, only the MMRM analyses with the standardised mean differences (Hedges' g) are used by the G-BA. However, there are uncertainties because the endpoint surveys at the end of treatment and in the follow-up after 30 days were not included in the MMRM analyses.

The MMRM analyses show no significant difference between the intervention and control arms.

The overall morbidity endpoints show an advantage for treatment with encorafenib + cetuximab based on a relevantly lower burden of the symptom "diarrhoea".

Quality of life

In the BEACON CRC study, health-related quality of life was assessed using the functional scales of the EORTC QLQ-C30 questionnaire and the FACT-C questionnaire.
The questionnaire FACT-C consists of the tumour-generic part FACT-G and an indication-specific part. Because the results of the indication-specific part of the FACT-C are not usable because of deviations from the scoring algorithm, only the tumour-generic part of the questionnaire (FACT-G) was used here. The present responder analyses, operationalised as time to permanent deterioration, are not used because drop-out occurred significantly more frequently and earlier in patients in the control arm than in the intervention arm. The time to first deterioration in the control arm was potentially compared with the time to permanent deterioration in the intervention arm. Therefore, only the MMRM analyses with the standardised mean differences (Hedges' g) are used by the G-BA. However, there are uncertainties because the endpoint surveys at the end of treatment and in the follow-up after 30 days were not included in the MMRM analyses.

The total score of the tumour-generic questionnaire FACT-G as well as the endpoint physical well-being in particular show a statistically significant advantage for the intervention arm in the mean change. However, the 95% confidence intervals of the standardised mean difference (Hedges' g) are not completely outside the irrelevance range of −0.2 to 0.2. Consequently, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

In the functional scales of the EORTC QLQ-C30 questionnaire, a statistically significant difference is shown in the endpoint global health status in the mean change. However, the 95% confidence intervals of the standardised mean difference (Hedges' g) are not completely outside the irrelevance range of −0.2 to 0.2. Consequently, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

In the overall view, neither an advantage nor a disadvantage in health-related quality of life can be derived for encorafenib + cetuximab.

Side effects

Adverse events (AE in total)

In the BEACON CRC study, approx. 98.1% of patients in the intervention arm and approx. 98.4% of patients in the comparator arm experienced an adverse event. The results for the endpoint "total adverse events" are presented additionally.

Serious AE

With regard to patients affected by serious AE, the time-to-event analysis shows a statistically significant difference in favour of encorafenib + cetuximab.

Severe AE (CTCAE grade ≥ 3)

In the BEACON CRC study, approx. 57.4% of patients in the intervention arm and approx. 64.2% of patients in the comparator arm experienced a severe adverse event. The time-to-event analyses show an advantage for encorafenib + cetuximab.

Discontinuation because of AE

At the time of this data cut-off, 12% of patients in the intervention arm and 17.1% of patients in the comparator arm had discontinued treatment because of adverse events. The time-to-event analysis shows a statistically significant difference between the treatment groups in favour of encorafenib + cetuximab.

Specific AE

The results on specific adverse events show a statistically significant difference to the benefit of encorafenib + cetuximab in the system organ class (SOC) of skin and subcutaneous tissue diseases.

Overall, the results on side effects show exclusively positive effects for encorafenib + cetuximab. Therefore, a significant improvement in side effects is seen with treatment with encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab.

Overall assessment/conclusion

For the benefit assessment of encorafenib in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation who have received at least one prior systemic therapy, results from the BEACON CRC study on overall survival, morbidity, health-related quality of life, and side effects are available compared with treatment with irinotecan + cetuximab or FOLFIRI + cetuximab.

For the overall survival of patients, treatment with encorafenib + cetuximab shows a statistically significant prolongation. Taking into account the poor survival prognosis for patients with BRAF-mutated tumours and the advanced stage of disease and treatment, the extent of this is assessed as a significant improvement in therapeutic benefit.

In the endpoint category morbidity, an advantage for encorafenib + cetuximab is shown by a relevantly lower burden of the symptom “diarrhoea”.

In the endpoint category health-related quality of life, neither an advantage nor a disadvantage in health-related quality of life can be derived for encorafenib + cetuximab.

The results on side effects show only positive effects for encorafenib + cetuximab. Therefore, a significant improvement in side effects is seen with treatment with encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab.

Overall, based on the results available from the BEACON CRC study, a hint for a considerable additional benefit for encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab is identified.

Reliability of data (probability of additional benefit)

On the risk of bias of the study results

The present assessment is based on the results of the open-label, randomised BEACON CRC study.

The risk of bias is rated as high overall at the study level. This is due to the lack of blinding in the BEACON CRC study and the fact that 28 (13%) of the randomised patients in the control arm and 4 (2%) of the randomised patients in the intervention arm (i.e. a relevantly larger proportion of patients in the control arm) did not start the study treatment and were missing from the analyses of all endpoints except overall survival.

At the endpoint level, additional uncertainties in the certainty of results arise from the subjective collection of patient-reported endpoints in an open-label study design in the endpoint categories morbidity and health-related quality of life as well as the endpoint discontinuation because of AEs.

<u>On the implementation of the appropriate comparator therapy and transferability of the study results to the German healthcare context</u>

The implementation of the appropriate comparator therapy in the BEACON CRC study also generates major uncertainties in the reliability of data. Although irinotecan + cetuximab and FOLFIRI + cetuximab represent a treatment option in the context of patient-individual therapy, it cannot be assumed that a majority of patients in the therapeutic indication would be treated according to the control arm in the reality of care. Thus, the BEACON study only partially fulfils the requirement of a comparison against the current standard of care, although the BRAF mutation of the tumours was not used as a predictive factor for the choice of therapy.

Therefore, in the overall assessment, the reliability of data (probability of additional benefit) for the additional benefit is classified as a hint.

2.5 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient encorafenib:

“Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.”

The appropriate comparator therapy was a patient-individual therapy taking into account the general condition and the type and number of previous therapies, selecting from:

- 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab
- Capecitabine + oxaliplatin ± bevacizumab
- 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab
- Irinotecan ± cetuximab or panitumumab
- Trifluridine/tipiracil
- 5-fluorouracil ± bevacizumab
- Capecitabine ± bevacizumab

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For the benefit assessment, the pharmaceutical company submits the results of the randomised, open-label BEACON CRC study comparing encorafenib + cetuximab with cetuximab + irinotecan or cetuximab + FOLFIRI in the control arm.

For the overall survival of patients, treatment with encorafenib + cetuximab shows a statistically significant prolongation. Taking into account the poor survival prognosis for patients with

BRAF-mutated tumours and the advanced stage of disease and treatment, the extent of this is assessed as a significant improvement in therapeutic benefit.

In the endpoint category morbidity, an advantage for encorafenib + cetuximab is shown by a relevantly lower burden of the symptom “diarrhoea”.

In the endpoint category health-related quality of life, neither an advantage nor a disadvantage can be derived for encorafenib + cetuximab.

The results on side effects show only positive effects for encorafenib + cetuximab. Therefore, a significant improvement in side effects is seen with treatment with encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab.

Overall, based on the results available from the BEACON CRC study, a hint for a considerable additional benefit for encorafenib + cetuximab compared with irinotecan + cetuximab or FOLFIRI + cetuximab is identified.

2.6 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 approx. 525–1,233 patients reported by the pharmaceutical company is an underestimate overall. This is mainly due to the fact that the pharmaceutical company uses only the incidence but not the prevalence of patients with mKRK with a BRAF V600E mutation for the calculation. However, a relevant number of incident cases under therapy in the previous year can be assumed; these would therefore have to be taken into account. This is especially true because patients with only one previous therapy are also included in the therapeutic indication.

In its calculations, the pharmaceutical company takes into account only patients who have already received at least one second-line therapy, although the therapeutic indication also includes patients who have received only one previous therapy. This leads to an underestimation of the upper limit.

There are also uncertainties in determining the proportional value of the BRAF mutations. Because the pharmaceutical company uses the lower of the percentages available in the literature for the calculation, this also contributes to a potential underestimation of the patient numbers.

2.7 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 Braftovi (active ingredient: encorafenib) at the following publicly accessible link (last access: 10 December 2020):
https://www.ema.europa.eu/documents/product-information/braftovi-epar-product-information_de.pdf

Treatment with encorafenib in combination with cetuximab should be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with metastatic colorectal cancer.

2.8 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 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 different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average height: 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]

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

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				
Encorafenib	1 × daily	365	1	365
Cetuximab	1 × every 7 days	52.1	1	52.1
Appropriate comparator therapy				
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab				
FOLFOX 4				
Oxaliplatin	1 × on Day 1 of a 14-day cycle	12	1	12
Folinic acid	1 × on Day 1 + 2 of a 14-day cycle	12	2	24
5-fluorouracil	1 × on Day 1 + 2 of a 14-day cycle	12	2	24
Plus bevacizumab if necessary				
Bevacizumab	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
FOLFOX 6				
Oxaliplatin	1 × on Day 1 of a 14-day cycle	12	1	12
Folinic acid	1 × on Day 1 of a 14-day cycle	12	1	12
5-fluorouracil	1 × on Day 1 of a 14-day cycle	12	1	12

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
CAPOX (capecitabine + oxaliplatin) ± bevacizumab				
CAPOX				
Oxaliplatin	1 × on Day 1 of a 21-day cycle	8	1	8
Capecitabine	2 × on Day 1–14 of a 21-day cycle	8	14	112
Plus bevacizumab if necessary				
Bevacizumab	1 × on Day 1 of a 21-day cycle	17.4	1	17.4
FOLFIRI (5-fluorouracil, folinic acid, irinotecan) ± aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab[3]				
FOLFIRI				
Irinotecan	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Folinic acid	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
5-fluorouracil	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Plus aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab if necessary				
Ramucirumab	1 × on Day 1 of a 14-day cycle	26.1	1	26.1

[3] In view of different FOLFIRI protocols, the information from the product information for Cyramza® (ramucirumab; last revised May 2016) and Zaltrap® (aflibercept; last revised July 2019) as well as Peeters et al. 2010 is used as examples.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Aflibercept	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Bevacizumab	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Cetuximab	1 × every 7 days	52.1	1	52.1
Panitumumab	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Irinotecan ± cetuximab or panitumumab[4]				
Irinotecan monotherapy				
Irinotecan	1 × on Day 1 of a 21-day cycle	17.4	1	17.4
Irinotecan + cetuximab or panitumumab[5]				
Irinotecan	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Cetuximab	1 × every 7 days	52.1	1	52.1
Panitumumab	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Trifluridine/tipiracil				

[4] Peeters et al.: Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010 Nov 1; 28 (31): 4706–13. doi: 10.1200/JCO.2009.27.6055. Epub 2010 Oct 4. PMID: 20921462.
Format:

[5] Sakai et al.: Randomised phase II study of panitumumab plus irinotecan versus cetuximab plus irinotecan in patients with KRAS wild-type metastatic colorectal cancer refractory to fluoropyrimidine, irinotecan and oxaliplatin (WJOG 6510G). Eur J Cancer. 2020 Aug; 135: 11–21. doi: 10.1016/j.ejca.2020.04.014. Epub 2020 Jun 8. PMID: 32526634.
Form

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Trifluridine/tipiracil	2 × daily on Days 1–5 and 8–12 of a 28-day cycle	13	10	130
5-fluorouracil ± bevacizumab				
5-fluorouracil (de Gramont)				
Folinic acid	1 × on Day 1 + 2 of a 14-day cycle	26.1	2	52.2
5-fluorouracil	1 × on Day 1 + 2 of a 14-day cycle	26.1	2	52.2
Plus bevacizumab if necessary				
Bevacizumab	1 × on Day 1 of a 14-day cycle	26.1	1	26.1
Capecitabine ± bevacizumab				
Capecitabine	2 × daily on Day 1–14 of a 21-day cycle	17.4	14	243.6
Plus bevacizumab if necessary				
Bevacizumab	1 × on Day 1 of a 21-day cycle	17.4	1	17.4

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					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Encorafenib	300 mg	300 mg	4 × 75 mg	365	1,460 × 75 mg
Cetuximab	Initial dose in Week 1: 400 mg/m² BSA	760 mg	1 × 500 mg +	1	52.1 × 500 mg +
			3 × 100 mg		3 × 100 mg
	From Week 2: 250 mg/m² BSA	475 mg	1 × 500 mg	51.1	
Appropriate comparator therapy					
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab					
FOLFOX 4					
Oxaliplatin	85 mg/m²	161.5 mg	1 × 200 mg	12	12 × 200 mg
Folinic acid	200 mg/m²	380 mg	1 × 500 mg	24	24 × 500 mg
5-fluorouracil	400 mg/m²	760 mg	1 × 1,000 mg	24	72 × 1,000 mg
	600 mg/m²	1,140 mg	2 × 1,000 mg		
Plus bevacizumab if necessary					
Bevacizumab	5 mg/kg BW -	385 mg –	1 × 400 mg –	26.1	26.1 × 400 mg –
	10 mg/kg BW	770 mg	2 × 400 mg		52.2 × 400 mg
FOLFOX 6					
Oxaliplatin	85 mg/m²	161.5 mg	1 × 200 mg	12	12 × 200 mg
Folinic acid	400 mg/m²	760 mg	1 × 800 mg	12	12 × 800 mg
5-fluorouracil	400 mg/m²	760 mg	1 × 1,000 mg	12	72 × 1,000 mg
	2,400 mg/m²	4,560 mg	5 × 1,000 mg		
CAPOX (capecitabine + oxaliplatin) ± bevacizumab					
CAPOX					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Oxaliplatin	130 mg/m²	247 mg	1 × 200 mg + 1 × 50 mg	8	8 × 200 mg + 8 × 50 mg
Capecitabine	1,000 mg/m² = 1,900 mg	3,800 mg	8 × 500 mg	112	896 × 500 mg
Plus bevacizumab if necessary					
Bevacizumab	7.5 mg/kg BW	577.5 mg	1 × 400 mg + 2 × 100 mg	17.4	17.4 × 400 mg + 34.8 × 100 mg
FOLFIRI (5-fluorouracil, folinic acid, irinotecan) ± aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab					
FOLFIRI					
Irinotecan	180 mg/m²	342 mg	1 × 300 mg + 2 × 40 mg	26.1	26.1 × 300 mg + 52.2 × 40 mg
Folinic acid	400 mg/m²	760 mg	1 × 800 mg	26.1	26.1 × 800 mg
5-fluorouracil	400 mg/m² 2,400 mg/m²	760 mg 4,560 mg	1 × 1,000 mg 5 × 1,000 mg	26.1	156.6 × 1,000 mg
Plus aflibercept or ramucirumab or bevacizumab or cetuximab or panitumumab if necessary					
Ramucirumab	8 mg/kg	616 mg	1 × 500 mg + 2 × 100 mg	26.1	26.1 × 500 mg + 52.2 × 100 mg
Aflibercept	4 mg/kg	308 mg	2 × 200 mg	26.1	52.2 × 200 mg
Bevacizumab	5 mg/kg BW	385 mg	1 × 400 mg	26.1	26.1 × 400 mg
Cetuximab	Initial dose in Week 1: 400 mg/m² BSA	760 mg	1 × 500 mg +	1	52.1 × 500 mg +

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
			3 × 100 mg		3 × 100 mg
	From Week 2:	475 mg	1 × 500 mg	51.1	
Panitumumab	6 mg/kg BW	462 mg	1 × 400 mg +	26.1	26.1 × 400 mg +
			1 × 100 mg		26.1 × 100 mg
Irinotecan ± cetuximab or panitumumab					
Irinotecan monotherapy					
Irinotecan	350 mg/m^2	665 mg	1 × 500 mg + 2 × 100 mg	17.4	17.4 × 500 mg + 34.8 × 100 mg
Irinotecan + cetuximab or panitumumab					
Irinotecan	150 mg/m^2	285 mg	1 × 300 mg	26.1	26.1 × 300 mg
Cetuximab	Initial dose in Week 1: 400 mg/m^2 BSA	760 mg	1 × 500 mg +	1	52.1 × 500 mg +
			3 × 100 mg		3 × 100 mg
	From Week 2:	475 mg	1 × 500 mg	51.1	
Panitumumab	6 mg/kg BW	462 mg	1 × 400 mg +	26.1	26.1 × 400 mg +
			1 × 100 mg		26.1 × 100 mg
Trifluridine/tipiracil					
Trifluridine/tipiracil	35 mg/m^2	65 mg	6 × 15 mg + 2 × 20 mg	130	780 × 15 mg + 260 × 20 mg
5-fluorouracil ± bevacizumab					
5-fluorouracil (de Gramont)					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Folinic acid	200 mg/m²	380 mg	1 × 500 mg	52.2	52.2 × 500 mg
5-fluorouracil	400 mg/m²	760 mg	1 × 1,000 mg	52.2	156.6 × 1,000 mg
	600 mg/m²	1,140 mg	2 × 1,000 mg		
Plus bevacizumab if necessary					
Bevacizumab	5 mg/kg BW	385 mg	1 × 400 mg	26.1	26.1 × 400 mg
Capecitabine ± bevacizumab					
Capecitabine	1,250 mg/m² = 2,375 mg	4,600 mg	8 × 500 mg + 2 × 300 mg	243.6	1,948.8 × 500 mg + 487.2 × 300 mg
Plus bevacizumab if necessary					
Bevacizumab	7.5 mg/kg BW	577.5 mg	1 × 400 mg + 2 × 100 mg	17.4	17.4 × 400 mg + 34.8 × 100 mg

Costs:

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

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					
Encorafenib 75 mg	168 HC	€ 6,775.43	€ 1.77	€ 393.68	€ 6,379.98

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
Cetuximab 500 mg	1 IS	€ 1,454.38	€ 1.77	€ 81.99	€ 1,370.62
Cetuximab 100 mg	1 IS	€ 299.49	€ 1.77	€ 16.40	€ 281.32
Appropriate comparator therapy					
Aflibercept 200 mg	1 CIS	€ 750.23	€ 1.77	€ 0.00	€ 748.46
Bevacizumab 100 mg	1 CIS	€ 386.74	€ 1.77	€ 21.35	€ 363.62
Bevacizumab 400 mg	1 CIS	€ 1,513.90	€ 1.77	€ 85.42	€ 1,426.71
Capecitabine 300 mg[6]	30 FCT	€ 35.18	€ 1.77	€ 1.98	€ 31.43
Capecitabine 500 mg[6]	120 FCT	€ 147.75	€ 1.77	€ 11.11	€ 134.87
Capecitabine 500 mg[6]	60 FCT	€ 85.20	€ 1.77	€ 6.04	€ 77.39
Cetuximab 500 mg	1 IS	€ 1,454.38	€ 1.77	€ 81.99	€ 1,370.62
Cetuximab 100 mg	1 IS	€ 299.49	€ 1.77	€ 16.40	€ 281.32
5-fluorouracil 1,000 mg[6]	5 SFI	€ 36.24	€ 1.77	€ 2.07	€ 32.40
5-fluorouracil 1,000 mg[6]	1 SFI	€ 15.98	€ 1.77	€ 0.42	€ 13.79
Folinic acid 500 mg[6]	10 IIS	€ 1,885.14	€ 1.77	€ 153.10	€ 1,730.27
Folinic acid 500 mg[6]	5 SFI	€ 948.38	€ 1.77	€ 76.08	€ 870.53
Folinic acid 500 mg[6]	1 SFI	€ 195.63	€ 1.77	€ 15.00	€ 178.86
Folinic acid 800 mg[6]	5 SFI	€ 1,461.00	€ 1.77	€ 117.60	€ 1,341.63
Folinic acid 800 mg[6]	1 SFI	€ 296.70	€ 1.77	€ 23.20	€ 271.73
Irinotecan 100 mg	1 CIS	€ 191.18	€ 1.77	€ 8.78	€ 180.63
Irinotecan 300 mg	1 CIS	€ 559.20	€ 1.77	€ 71.20	€ 486.23
Irinotecan 500 mg	1 CIS	€ 916.16	€ 1.77	€ 44.08	€ 870.31
Oxaliplatin 200 mg	1 CIS	€ 388.99	€ 1.77	€ 18.41	€ 368.81
Oxaliplatin 200 mg	1 CIS	€ 612.19	€ 1.77	€ 29.28	€ 581.14
Oxaliplatin 50 mg	1 CIS	€ 160.50	€ 1.77	€ 7.29	€ 151.44
Panitumumab 400 mg	1 CIS	€ 2,501.51	€ 1.77	€ 143.28	€ 2,356.46
Panitumumab 100 mg	1 CIS	€ 641.42	€ 1.77	€ 35.82	€ 603.83
Ramucirumab 100 mg	1 CIS	€ 429.79	€ 1.77	€ 23.80	€ 404.22
Ramucirumab 500 mg	1 CIS	€ 2,087.10	€ 1.77	€ 119.00	€ 1,966.33
Trifluridin/tipiracil 15 mg	60 FCT	€ 2,289.28	€ 1.77	€ 0.00	€ 2,287.51
Trifluridin/tipiracil 20 mg	60 FCT	€ 3,033.72	€ 1.77	€ 0.00	€ 3,031.95

[6] Fixed reimbursement rate

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
Abbreviations: FCT: film-coated tablets; HC: hard capsules; CIS: concentrate for the preparation of an infusion solution; IIS: injection/infusion solution; SFI: solution for injection; IS: solution for infusion					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 December 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 assessed 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.

According to the product information of cetuximab (Erbitux®), patients must be pretreated with an antihistamine and a corticosteroid at least 1 h before the first infusion of cetuximab. This premedication is also recommended before all further infusions. The product information does not provide any further details in this respect; the costs necessary for premedication can therefore not be quantified.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents 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 are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the *Hilfstaxe*. The cost representation is based on the pharmacy sales price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers and carrier solutions according to the regulations in 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

At its session on 12 November 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the European Medicines Agency (EMA) granted the positive opinion, a review of the appropriate comparator therapy defined by the G-BA at the time of the consultation on the basis of the planned/applied therapeutic indication took place on 4 June 2020.

On 30 June 2020, the pharmaceutical company submitted a dossier for the benefit assessment of encorafenib in combination with cetuximab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 June 2020 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 encorafenib in combination with cetuximab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 October 2020. The deadline for submitting written statements was 22 October 2020.

The oral hearing was held on 9 November 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 8 December 2020, and the proposed resolution was approved.

At its session on 17 December 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 November 2019	Determination of the appropriate comparator therapy
Working group Section 35a	4 June 2020	Review of the appropriate comparator therapy after granting the positive opinion
Working group Section 35a	3 November 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	9 November 2020	Conduct of the oral hearing,
Working group Section 35a	17 November 2020 1 December 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure

Subcommittee on Medicinal Products	8 December 2020	Concluding discussion of the draft resolution
Plenum	17 December 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 December 2020

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

Prof. Hecken