Gemeinsamer Bundesausschuss

# Justification

for the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Zanidatamab

(biliary tract cancer, HER2+ [IHC3+], pretreated)

From 6 August 2026

**Contents**

## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit of an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with Chapter 5, Sections 5 et seqq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company shall provide evidence - within three months of being requested to do so by the G-BA - in accordance with Chapter 5, Section 5, paragraphs 1 to 6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy specified by the G-BA in accordance with Chapter 5, Section 6 VerfO, and in this evidence, demonstrate the additional benefit over the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decide whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determine an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover limit according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient zanidatamab on 15 February 2026 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to 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 of the Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 12 February 2026.

Zanidatamab for the treatment of biliary tract cancer is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 May 2026 together with the IQWiG assessment on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA have adopted their resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G26-05) 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 have assessed the studies relevant to the marketing authorisation on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 to 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of zanidatamab.

### 2.1 Additional benefit of the medicinal product

#### 2.1.1 Approved therapeutic indication of zanidatamab (Ziihera) in accordance with the product information

Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy.

[1]General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

**Therapeutic indication of the resolution (resolution of 6 August 2026):**

See the approved therapeutic indication

### 2.1.2 Extent of the additional benefit and significance of the evidence

Adults with unresectable locally advanced or metastatic HER2-positive (IHC 3+) biliary tract cancer previously treated with at least one prior line of systemic therapy

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The pharmaceutical company submitted data from the HERIZON-BTC-01 approval study and an indirect comparison with an external comparator population for the assessment of the extent of the additional benefit of zanidatamab in the therapeutic indication "Treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy".

*HERIZON-BTC-01 study*

The HERIZON-BTC-01 study is a multicentre, open-label, single-arm phase IIb study investigating the anti-tumour activity of zanidatamab in adults with HER2-amplified, unresectable, advanced or metastatic biliary tract cancer. Eligible participants were adults aged ≥ 18 years with histologically or cytologically confirmed biliary tract cancer, gallbladder cancer, intrahepatic cholangiocarcinoma or extrahepatic cholangiocarcinoma. Furthermore, patients were not to be eligible for curative treatment, including resection, transplantation or ablation, and were required to have progressive disease following at least one prior line of therapy with gemcitabine-containing systemic chemotherapy in the advanced stage of the disease. Study participants were also required to have an ECOG performance status ≤ 1 and must not have had any untreated symptomatic CNS metastases or have undergone radiotherapy for CNS metastases within 4 weeks prior to the start of study treatment. A total of 87 patients were enrolled in the study.

The study was conducted between 2020 and 2024 at 32 study sites in Asia, Europe, as well as North and South America.

The primary endpoint of the study was the confirmed objective response rate. A total of 3 data cut-offs are available for the study: First, pre-specified data cut-off from 10 October 2022, the 2nd data cut-off from 28 July 2023 and the final data cut-off from 28 July 2024.

The final data cut-off from 28 July 2024 was used for the benefit assessment.

On the relevant patient population

The relevant post-hoc sub-population with overexpressed HER2 amplification (IHC 3+) in accordance with the authorisation population was used for the benefit assessment. The sub-population relevant to the benefit assessment comprises 62 patients.

*Indirect comparison between HERIZON-BTC-01 and individual patient data*

In the benefit assessment dossier, the pharmaceutical company also presented an indirect comparison – without a bridge comparator – between data from the relevant sub-population with HER2 amplification (IHC 3+) from the pivotal HERIZON-BTC-01 study and individual patient data.

JZP598_515 is a comparative analysis of the relevant sub-population from the HERIZON-BTC-01 study and individual patient data to determine the endpoints of overall survival and progression-free survival. The study protocol cited two data sources: the Flatiron Health Research Analytic Database (FHRD) and the European Network for the Study of Cholangiocarcinoma (ENSCCA). However, the sole data source for the analysis of individual patient data is the FHRD, in the form of retrospective observational data based on electronic case records from the USA. The ENSCCA data source is a European registry that tracks patients through an observational study. In the dossier, the pharmaceutical company did not provide any justification for relying solely on the FHRD data. The statement included information indicating that no analysable ENSCCA data were available at the time the dossier was prepared. Accordingly, the analysis of the ENSCCA data identified 11 HER2-positive patients, of whom, however, only 2 received second-line therapy. Against this background, there are therefore still no ENSCCA data available for analysis.

To select the comparator population, 29,000 suitable electronic case records were identified from the FHRD using artificial intelligence/ machine learning (AI/ML)-based methods applied to structured and unstructured data; these were then reviewed by medical experts with regard to diagnosis, evidence of HER2 testing and the initiation of second-line therapy. The following inclusion and exclusion criteria were then operationalised in three stages: Stage 1: selected subjects with a BTC diagnosis and HER2-positive overexpression (IHC 3+) and systemic second-line therapy. At the 2$^{nd}$ stage, subjects with an ECOG-PS > 1 as determined by natural language processing (NLP) and those with brain metastases were excluded. At a 3$^{rd}$ stage, further inclusion and exclusion criteria were applied. The pharmaceutical company identified a total of 29 subjects with an HER2-positive IHC status of 3+; of these, 12 subjects received chemotherapy in both first-line and second-line therapy. The 2$^{nd}$ stage was used by the pharmaceutical company for the indirect comparison. The observation period for individual patient data begins with the initiation of second-line therapy, which was defined as any second line of systemic therapy that differs from the first-line therapy.

The pharmaceutical company carried out a review to identify confounders and assessed their relevance. The following confounders were included in the propensity score model: Age (at the start of second-line therapy); tumour type; pre-existing chronic liver disease; sex.

To estimate a treatment effect, the Standard Morbidity Ratio (SMR) was calculated on the basis of propensity scores and used as the weighting method. To this end, the external control arm was reweighted to be representative of the study cohort.

Assessment

With regard to the choice of the data source, no systematic search for potential data sources in the therapeutic indication could be identified.

AI/ML-based methods were used to extract individual patient data from the FHRD data source. On the basis of the available documents, it cannot be assumed that the statistical methods used and the manual verification of individual variables, such as stage of the disease or laboratory parameters, resulted in complete and sufficiently comparable BTC-specific information for the comparator population being extracted from the FHRD in comparison with the HERIZON-BTC-01 cohort.

In the selection of the comparator population, the inclusion and exclusion criteria were applied in several stages, modelled on the HERIZON-BTC-01 study; however, it was not possible to operationalise several inclusion and exclusion criteria. In addition to relevant clinical parameters for treatment allocation (such as laboratory values and infections), the ECOG-PS and brain metastases could not be fully operationalised, meaning that some relevant information is missing. If the pharmaceutical company had taken further inclusion criteria, such as adequate liver function and haematological function, into account, this might have restricted the comparator population even further, which is why some of the 12 subjects identified might not have been suitable for participation in the HERIZON-BTC-01 study on the basis of their liver or haematological function.

Furthermore, the propensity score model used was unable to take account of the missing inclusion and exclusion criteria due to the choice of confounders.

An additional significant source of uncertainty is that the two compared cohorts might have systematically different index time points, or "time zeros", meaning second-line therapy was initiated at different stages of disease progression.

Overall, the comparability of the external control population and the relevant sub-population of the HERIZON-BTC-01 study has not been sufficiently demonstrated on the basis of the available documents.

Furthermore, some of the confounders that were identified and assessed as relevant were not included in the propensity score model. SMR weighting was used as the adjustment method; however, its results cannot be meaningfully interpreted due to the incompleteness of the propensity scores used. Incidentally, the analysis is based on a sample size of just 12 subjects.

Following the oral hearing, the pharmaceutical company submitted the effect estimator (hazard ratio) for the naïve indirect comparison of the relevant sub-population with HER2 amplification of IHC 3+ and individual patient data with systemic chemotherapy from the FHRD for the endpoint of overall survival. In this regard, the indirect comparison without weighting showed no statistically significant difference in overall survival.

In view of the aforementioned reasons, the submitted indirect comparison between the sub-population with HER2 amplification of IHC 3+ from the HERIZON-BTC-01 study - relevant for the benefit assessment - and the external comparator population is assessed as failing to provide a data basis sufficient to derive reliable statements regarding the quantification of the additional benefit. The presented indirect comparison without bridge comparator is therefore not used for the present assessment.

<u>On the results of the HERIZON-BTC-01 study</u>

<u>Mortality</u>

In the HERIZON-BTC-01 study, overall survival was defined as the period from the first dose of the study medication until death from any cause.

At the time the data cut-off was submitted for the benefit assessment, a total of 45 subjects (72.6%) had died. Overall survival at month 12 was 65.0%. The median survival time was 18.1 months.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Morbidity

*Confirmed objective response rate (cORR)*

In the HERIZON-BTC-01 study, *cORR* is a component of the tumour response endpoint and is defined as the achievement of a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria, based on the assessment of CT and/or MRI scans by an independent review committee (ICR).

32 study participants (51.6%) showed a cORR.

The assessment of cORR was carried out by means of an independent radiological review and was therefore not based on symptoms, but primarily on imaging procedures. For this reason, this endpoint is classified as not patient-relevant.

As this is the primary endpoint of the HERIZON-BTC-01 study, the results are presented additionally.

Regardless of this, the results of the HERIZON-BTC-01 study on the cORR endpoint do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

*Progression-free survival (PFS)*

The PFS was assessed as a secondary endpoint. In the study, the PFS endpoint was operationalised as the time between the first dose of the study medication and either radiologically confirmed disease progression according to RECIST 1.1 criteria or death, as assessed by an independent review committee (ICR).

The present PFS endpoint is a composite endpoint consisting of endpoints from the "mortality" and "morbidity" categories. The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component of disease progression was assessed according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Notwithstanding this, it is not possible to carry out a comparative assessment based on the results of the HERIZON-BTC-01 study for the PFS endpoint due to the absence of a control group.

*Pain using BPI-SF*

The "pain" endpoint was assessed using the measurement tool of Brief Pain Inventory – Short Form (BPI-SF) ("pain intensity" and "impairment due to pain") on a scale from 0 ("no pain or no impairment") to 10 ("worst pain imaginable or most severe impairment").

8 study participants (18.6%) showed a deterioration in "pain intensity" by ≥ 15% of the scale range compared with baseline (mean value of items 3 to 6). 19 study participants (30.6%)

showed a deterioration in "impairment due to pain" by ≥ 15% of the scale range compared with baseline (items 9a to 9g).

The overall statement on the extent of the additional benefit remains unaffected by this due to the absence of a control group, and no statement on the extent of the additional benefit can be derived.

*Health status using EQ-5D VAS*

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

9 patients (14.5%) showed a deterioration by ≤ 15 points at the end of treatment.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

Quality of life

No data on health-related quality of life were assessed.

Side effects

*Total adverse events (AEs)*

Almost all patients experienced an adverse event (98.4%). These are only presented additionally.

*Serious adverse events (SAEs)*

33 out of 62 patients (53.3%) had at least one serious adverse event.

*Severe adverse events (CTCAE grade ≥ 3)*

At least one severe AE with CTCAE grade ≥ 3 occurred in 40 out of 62 patients (64.5%) of the relevant sub-population.

*Therapy discontinuation due to adverse events*

In 2 patients (3.2%), an adverse event occurred that led to the discontinuation of the study medication.

*Specific AEs*

Severe adverse events with CTCAE grade ≥ 3 with an incidence ≥ 10% of patients by system organ class (SOC) were gastrointestinal disorders (24.2%), hepatobiliary disorders (19.4%), investigations (22.6%), infections and infestations (19.4%), blood and lymphatic system disorders (17.7%) and vascular disorders (11.3%).

Hepatobiliary disorders (19.4%), gastrointestinal disorders (17.7%) and infections and infestations (19.4 %) occurred as serious adverse events with an incidence ≥ 10% of patients by system organ class (SOC).

In summary, no conclusions can be drawn on the extent of the additional benefit for the side effects category due to the absence of a control group.

Overall assessment

On the one hand, data on the categories of mortality, morbidity, and side effects are available from the label-enabling, single-arm HERIZON-BTC-01 study for the benefit assessment of zanidatamab for the treatment of adults with unresectable locally advanced or metastatic

HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy. As this study does not allow for a comparative assessment, no statement can be made on the extent of the additional benefit on the basis of the HERIZON-BTC-01 study.

On the other, the pharmaceutical company presented an indirect comparison - without a bridge comparator - between data from the relevant sub-population with HER2 amplification of IHC 3+ from the HERIZON-BTC-01 study and a comparator population derived from retrospective, individual patient data. On the basis of the available documents, it cannot be assumed that, compared with the HERIZON-BTC-01 cohort, complete and sufficiently comparable BTC-specific information has been extracted for the comparator population, as a large number of the inclusion and exclusion criteria from the HERIZON-BTC-01 study could not be operationalised when selecting the comparator population. This is primarily due to the fact that relevant clinical parameters for treatment allocation, such as the ECOG-PS and brain metastases, could not be taken into account fully, or at all.

An additional significant source of uncertainty is that the two compared cohorts might have systematically different index time points, or "time zeros", meaning second-line therapy was initiated at different stages of disease progression.

Overall, the comparability of the external control population and the relevant sub-population of the HERIZON-BTC-01 study has not been sufficiently demonstrated on the basis of the available documents.

Furthermore, some of the confounders that were identified and assessed as relevant were not included in the propensity score model. Incidentally, the analysis is based on a sample size of just 12 subjects.

Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on data from the single-arm phase IIb HERIZON-BTC-01 study, which does not allow for a comparative assessment. Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

Thus, a comparative assessment is not possible overall, which is why the reliability of data is rated in the hint category.

### 2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Ziihera with the active ingredient zanidatamab.

Zanidatamab has been approved as an orphan drug under exceptional circumstances for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC 3+) biliary tract cancer previously treated with at least one prior line of systemic therapy.

On the one hand, data on the categories of mortality, morbidity and side effects are available from the label-enabling single-arm HERIZON-BTC-01 study for the benefit assessment. As this

study does not allow for a comparative assessment, no statement can be made on the extent of the additional benefit on the basis of the HERIZON-BTC-01 study.

On the other, the pharmaceutical company presented an indirect comparison - without a bridge comparator - between the relevant sub-population of the HERIZON-BTC-01 study and retrospective, individual patient data.

In the selection of the comparator population, it was not possible to operationalise several inclusion and exclusion criteria from the HERIZON-BTC-01 study.

An additional significant source of uncertainty is that the second-line therapy might have been initiated at different stages of disease progression in the two cohorts being compared.

Overall, the comparability of the external control population and the relevant sub-population of the HERIZON-BTC-01 study has not been sufficiently demonstrated on the basis of the available documents.

Furthermore, some of the confounders that were identified and assessed as relevant were not included in the propensity score model. Incidentally, the analysis is based on a sample size of just 12 subjects.

Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

The reliability of data of the additional benefit identified is classified as a "hint".

## 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 is based on the information provided by the pharmaceutical company in the benefit assessment dossier. The pharmaceutical company's calculation of the patient numbers in the dossier is uncertain overall at the lower limit and tends to be an overestimation of the upper limit.

There are uncertainties regarding the percentage of patients with unresectable or metastatic disease at the time of initial diagnosis for all entities (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary cancer). In the case of intrahepatic cholangiocarcinoma, there are uncertainties regarding the lower and upper limits, particularly as a higher-level diagnostic code is used and it is generally assumed that patients at stage III are inoperable. For the other tumour entities, the uncertainty relates primarily to the use of a percentage value across tumour entities based on a review.

When determining the percentage of patients with recurrence following tumour resection, uncertainty arises from the fact that the pharmaceutical company allocates all recurrences to the locally advanced or metastatic treatment setting. Furthermore, when deriving the data for the respective tumour entities, not all types of recurrence relevant to the therapeutic indication are taken into account, or non-entity-specific information is used.

When considering the percentage of patients with intrahepatic and extrahepatic cholangiocarcinoma who received first-line chemotherapy directly, the percentage of patients receiving first-line chemotherapy is lower, particularly when patients undergoing active

palliative care are taken into account. Furthermore, for all tumour entities, reference is made to general information on cholangiocarcinoma or biliary tract cancer, and with regard to the percentages of patients receiving first-line therapy, unclear data from the publication by Rimassa et al. are used.

The data on first-line chemotherapy for patients with recurrence following tumour resection as well as intrahepatic and extrahepatic cholangiocarcinoma is uncertain, as the analysis was limited exclusively to patients with intrahepatic cholangiocarcinoma and distant metastases. The percentages of patients with gallbladder cancer or ampullary cancer are also subject to uncertainty, as the percentages in some cases included patients with unresectable cancers and generalised data on biliary tract cancer were used.

With regard to the percentage of patients who received second-line chemotherapy following first-line therapy, the uncertainties relate in particular to the exclusion of patients whose disease progressed without having received second-line therapy and the exclusion of patients in higher lines of therapy.

The percentages given for subjects with HER2 overexpression and an IHC score of 3+ are uncertain overall, particularly given the unclear transferability of the data to the target population. Furthermore, the percentages of patients with an IHC score of 3+ are based on very small sample sizes; percentages across tumour entities were used; and the publications consulted employed different reference variables for HER2 positivity.

### 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 Ziihera (active ingredient: zanidatamab) at the following publicly accessible link (last access: 20 July 2026):

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

Treatment with zanidatamab should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and gastroenterology and other specialists from other specialist groups participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with biliary tract cancer.

This medicinal product was approved under "exceptional circumstances". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information where 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: 1 June 2026).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

The annual treatment costs shown refer to the first year of treatment.

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 from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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 | | | | |
| Zanidatamab | Continuously; every 14 days | 26.1 | 1 | 26.1 |

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 comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "2025 Microcensus – body measurements of the population" were applied (average body height: 1.73 m; average body weight: 78.3 kg). This results in a body surface area of 1.92 m² (calculated according to Du Bois 1916)[2].

| 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 | | | | | |
| Zanidatamab | 20 mg/kg = 1,566 mg | 1,566 mg | 6 x 300 mg | 26.1 | 156.6 x 300 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 in accordance with Section 130 and Section 130a 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

[2] Federal Health Reporting. Average body measurements of the population (2025, both sexes), www.gbe-bund.de

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**Costs of the medicinal products:**

| Designation of the therapy | Packaging 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 | | | | | |
| Zanidatamab 300 mg | 2 PCI | € 8,402.55 | € 1.77 | € 476.58 | € 7,924.20 |
| PCI = powder for a concentrate for the preparation of an infusion solution | | | | | |

LAUER-TAXE® last revised: 1 June 2026

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

The calculation of the additionally required SHI services is based on the fee structure items (FSI) as of the 2nd quarter of 2026 of the uniform value scale (UVS 2026/Q2).

Echocardiography

Due to the risk of left ventricular functional impairments, an echocardiogram is required before starting treatment with zanidatamab. During treatment, the left ventricle should be assessed at regular intervals using echocardiography.

| Echocardiography | Costs after deduction of statutory rebates | Treatment days/ year | Costs/ patient/ year |
|---|---|---|---|
| **Medicinal product to be assessed** | | | |
| Zanidatamab; echocardiography<br>Initially and 1 x per quarter | | | |
| Echocardiography (M-mode and B-mode methods)<br>FSI 33020 | € 31.21 | 4.0 | € 124.84 |

*Other SHI services:*

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate 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 currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-apply unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail 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 in accordance with the regulations in Annex 3 of the Hilfstaxe.

## 3. Bureaucratic costs calculation

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

## 4. Process sequence

On 12 February 2026, the pharmaceutical company submitted a dossier for the benefit assessment of zanidatamab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 May 2026 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de) together with IQWiG's assessment of treatment costs and patient numbers, thus initiating the written statement procedure. The deadline for submitting written statements was 5 June 2026.

The oral hearing was held on 22 June 2026.

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 Subcommittee’s session on 28 July 2026, and the draft resolution was conclusively discussed.

At their session on 6 August 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Gemeinsamer Bundesausschuss

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 26 November 2024 | Information of the benefit assessment of the G-BA |
| Working group Section 35a | 17 June 2026 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 22 June 2026 | Conduct of the oral hearing |
| Working group Section 35a | 30.06.2026; 14.07.2026 | Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 28 July 2026 | Concluding discussion of the draft resolution |
| Plenum | 6 August 2026 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 6 August 2026

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

Dr Optendrenk