Gemeinsamer Bundesausschuss

Justification

of 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 Sacituzumab govitecan (breast cancer, triple-negative, at least 2 prior therapies)

of 19 May 2022

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1. Legal basis

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

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient sacituzumab govitecan in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 December 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 November 2021.

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 1 March 2022, 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 sacituzumab govitecan compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of sacituzumab govitecan.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Sacituzumab govitecan (Trodelvy) in accordance with the product information

Trodelvy as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.

Therapeutic indication of the resolution (resolution of 19 May 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease

– capecitabine

or

– eribulin

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

or

– vinorelbine

or

– an anthracycline *or* taxane-containing therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment)

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

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

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

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

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

on 1. In the present therapeutic indication, in addition to sacituzumab govitecan, medicinal products containing the active ingredients 5-fluorouracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, eribulin, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, nab-paclitaxel, vinblastine, vincristine, vinorelbine, olaparib and talazoparib are approved.

on 2. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Eribulin: resolution of 22 January 2015
- Olaparib: resolution of 16 January 2020
- Talazoparib: resolution of 20 November 2020

Annex VI to Section K of the Pharmaceuticals Directive - Active ingredients that cannot be prescribed in applications beyond the scope of the marketing authorisation (off-label use):

- Gemcitabine in monotherapy for breast cancer in women

Guideline on hospital examination and treatment methods (guideline on hospital treatment methods):

- Proton therapy for breast cancer

on 3. A non-medicinal treatment cannot be considered in the present therapeutic indication. This does not affect the implementation of radiotherapy as a palliative patient-individual treatment option.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

In view of the fact that the therapeutic indication refers to triple-negative receptor status, endocrine therapies and therapies indicated exclusively for HER2-positive breast cancer are not considered.

Furthermore, it is assumed that the patients have usually received taxane and/or anthracycline-based chemotherapy as part of the prior therapy.

In addition, at this time, it is assumed that patients with genomic BRCA1/2 mutations will not be eligible for BRCA-specific therapy at the time of treatment with sacituzumab govitecan.

According to current guidelines, for patients who were pretreated with an anthracycline and taxane-based chemotherapy, further cytotoxic chemotherapy is the current treatment standard in case of disease progression or relapse.

Primarily monotherapies should be used with regard to cytotoxic chemotherapies. Polychemotherapy is considered indicated only in cases of more severe symptoms, rapid tumour growth and aggressive tumour behaviour.

Treatment with anthracyclines and taxanes can be considered for patients who have not yet received anthracycline and/or taxane-containing therapy or also as re-therapy in the case of corresponding individual conditions.

Of the active ingredients primarily mentioned in various guidelines, besides taxanes and anthracyclines, capecitabine, vinorelbine and eribulin are approved for use as monotherapy in the present therapeutic indication.

For the treatment of patients who have experienced further progression after at least one course of chemotherapy for the treatment of advanced breast cancer, the G-BA identified a hint for a considerable additional benefit of eribulin compared to monotherapy with capecitabine or vinorelbine for patients who can no longer be treated with taxanes or anthracyclines (resolution of 22 January 2015).

Taking into account the importance of eribulin in the current guideline recommendations in relation to other treatment options and in view of the restriction of the additional benefit to a part of the approved therapeutic indication, eribulin is considered to be an equally appropriate treatment option alongside capecitabine and vinorelbine.

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

2.1.3 Extent and probability of the additional benefit

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

Indication of a major additional benefit

Justification:

For the benefit assessment, the pharmaceutical company presents results from the open-label, randomised, multicentre phase III ASCENT study.

In the ASCENT study, sacituzumab govitecan was compared with a chemotherapy of the doctor's choice with the treatment options capecitabine, vinorelbine, eribulin or gemcitabine (each as monotherapy).

A total of 529 adult patients with locally advanced or metastatic triple-negative breast cancer who were pretreated with at least 2 systemic chemotherapies for unresectable, locally advanced or metastatic disease were enrolled in the study.

Patients were randomised in a 1:1 ratio to the intervention arm (n = 267) or the control arm (n = 262). Randomisation was stratified by region (North America vs rest of the world) and number of prior therapies for locally advanced or metastatic disease (2 or 3 vs > 3 therapies).

For the benefit assessment, the pharmaceutical company presents a relevant sub-population of the ASCENT study. This sub-population includes 224 (vs 221) patients for whom

capecitabine, vinorelbine or eribulin was selected as the active ingredient to be administered in an allocation to the control arm prior to randomisation. In the relevant sub-population, 8 (3.6%) vs 32 (14.3%) of the patients were not treated with the study medication.

Treatment with sacituzumab govitecan, capecitabine, eribulin or vinorelbine was largely in accordance with the product information, although dose adjustments were possible in the control arm according to local guidelines.

Study medication should be administered until disease progression, symptomatic deterioration, withdrawal of consent, therapy discontinuation as decided by the physician, death or unacceptable toxicity. Therapy could be continued after the first detection of disease progression, provided the patient benefited from it in the principal investigator's view. However, treatment had to be discontinued if subsequent imaging findings confirmed disease progression.

The primary endpoint is progression-free survival, secondary endpoints include overall survival and endpoints on morbidity, health-related quality of life and adverse events.

The completed study was conducted in 82 study sites across Europe and North America and was initiated in November 2017. No information is available at the end of the study.

For the benefit assessment, the results of the data cut-offs of 11.03.2020 and 25.02.2021 are used.

IQWiG's benefit assessment noted that subgroup analyses to investigate whether there were different effects of sacituzumab govitecan compared with each of the comparator therapy options would have been desirable. With its written statement, the pharmaceutical company submitted analyses of the study results on sacituzumab govitecan separately for the individual options of the appropriate comparator therapy used in the study. Based on these results, it is concluded that the results on the different treatment options can be interpreted in a summarised way.

Extent and probability of the additional benefit

Mortality

In the dossier, no evaluations were available for the endpoint of overall survival at the data cut-off of 25.02.2021 for the sub-population relevant to the assessment. With its written statement, the pharmaceutical company submitted this evaluation. This will be used for the present assessment.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of sacituzumab govitecan compared to capecitabine, vinorelbine and eribulin.

The extent of the prolongation achieved in overall survival is assessed as a very significant improvement.

Morbidity

Progression-free survival (PFS)

PFS was operationalised in the ASCENT study as the time from randomisation to the first observation of objective tumour progression or death, whichever occurs first.

Tumour response was assessed using radiological images according to RECIST version 1.1.

There is a statistically significant prolonged PFS to the advantage of sacituzumab govitecan compared to the appropriate comparator therapy.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already surveyed in the present study via the endpoint "overall survival" as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST 1.1 criteria). 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.

Symptomatology

Symptomatology was assessed in the ASCENT study using the symptom scales of the cancer-specific EORTC QLQ-C30 questionnaire.

The assessment of symptomatology was operationalised as time to first deterioration. Here, an increase in the score by ≥ 10 points compared to the start of the study was considered a clinically relevant deterioration.

With regard to the endpoints of nausea and vomiting, insomnia, appetite loss and constipation, there was no statistically significant difference between the treatment arms.

For the endpoints of fatigue, pain and dyspnoea, there is a statistically significant difference to the advantage of sacituzumab govitecan compared to the comparator therapy.

With regard to the endpoint of diarrhoea, there was a statistically significant difference to the disadvantage of sacituzumab govitecan compared to capecitabine, eribulin and vinorelbine.

In the overall analysis of the results, there are both advantages and disadvantages for sacituzumab govitecan with regard to symptomatology compared to the appropriate comparator therapy, whereby the positive effects of sacituzumab govitecan outweigh the disadvantages overall.

Quality of life

Health-related quality of life was assessed in the ASCENT study using the functional scales of the cancer-specific EORTC QLQ-C30 questionnaire.

The assessment of quality of life was operationalised as time to first deterioration. Here, a decrease in the score by ≥ 10 points compared to the start of the study was considered a clinically relevant deterioration.

For the endpoints of global health status, cognitive functioning and social functioning, there is no statistically significant difference between the treatment arms.

With regard to the endpoints of physical functioning, role functioning and emotional functioning, there was a statistically significant difference to the advantage of sacituzumab govitecan compared to capecitabine, eribulin and vinorelbine.

Overall, there are only positive effects of sacituzumab govitecan with regard to quality of life.

Side effects

Adverse events (AEs) in total

In the ASCENT study, adverse events occurred in both study arms in almost all patients enrolled. The results were only presented additionally.

Serious adverse events (SAE)

For the endpoint of SAE, there is a statistically significant difference to the advantage of sacituzumab govitecan compared to the comparator therapy.

Severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events (AE)

With regard to the endpoints of severe AEs and discontinuation due to AEs, there was no statistically significant difference between the treatment arms.

Specific adverse events

For the specific adverse events, both advantages and disadvantages are shown in detail.

For the endpoints of neuropathy (AEs), general disorders and administration site conditions (severe AEs) and respiratory, thoracic and mediastinal disorders (severe AEs), there was a statistically significant difference to the advantage of sacituzumab govitecan compared to capecitabine, eribulin or vinorelbine.

For the endpoints of gastrointestinal toxicity, neutropenia, metabolism and nutrition disorders (each severe AEs) and skin and subcutaneous tissue disorders (AEs), there is a statistically significant difference to the disadvantage of sacituzumab govitecan compared to the control arm.

For the endpoint of skin and subcutaneous tissue disorders (AEs), the subgroup analysis shows proof of an effect modification with regard to the age characteristic. For subjects aged < 65 years, there is a statistically significant difference to the disadvantage of sacituzumab govitecan, whereas for people aged ≥ 65 years there is no statistically significant difference. As this effect modification is not shown for further endpoints, the significance of the available subgroup results for the overall assessment of the additional benefit is considered inadequate.

The data on hand-foot syndrome submitted in the dossier as well as in the written statement procedure cannot be used, as the pharmaceutical company did not submit any time-to-event analyses, which are necessary for a meaningful interpretation of the results.

In the overall assessment of the results on the side effects, advantages as well as disadvantages can be determined for sacituzumab govitecan compared to capecitabine, eribulin and vinorelbine, whereby the positive effects of sacituzumab govitecan predominate overall.

Overall assessment

For the benefit assessment of sacituzumab govitecan for the treatment of unresectable or metastatic triple-negative breast cancer, in adults who have previously received two or more systemic therapies, including at least one for advanced disease, data on mortality, morbidity, quality of life and side effects are available for the relevant sub-population from the ASCENT study. The relevant sub-population includes patients for whom capecitabine, vinorelbine or eribulin was selected as the active ingredient to be administered prior to randomisation in case of allocation to the control arm.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of sacituzumab govitecan compared to capecitabine, eribulin or vinorelbine. The magnitude of the effect is assessed as a very significant improvement.

With regard to symptomatology, the EORTC QLQ-C30 shows several advantages and one disadvantage for sacituzumab govitecan compared with the comparator therapy.

With regard to quality of life, the EORTC QLQ-C30 shows only positive effects of sacituzumab compared to the appropriate comparator therapy.

For the endpoint category of side effects, an advantage of sacituzumab govitecan over capecitabine, eribulin or vinorelbine can be identified for SAE, as well as advantages and disadvantages for specific AEs in detail. In the overall assessment of the endpoint of side effects, the positive effects of sacituzumab govitecan predominate.

Overall, a previously unachieved major improvement in the therapy-relevant benefit compared to the appropriate comparator therapy is determined for sacituzumab govitecan, particularly against the background of the disease severity of triple-negative breast cancer and the poor prognosis of the patients, who are also already in a late line of therapy in the present therapeutic indication.

The overall assessment identifies a major additional benefit of sacituzumab govitecan in adults with unresectable or metastatic triple-negative breast cancer who have previously received two or more systemic therapies, including at least one for advanced disease.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the completed open-label, randomised, multicentre phase III ASCENT study.

Based on the information submitted by the pharmaceutical company in the dossier, the IQWiG rated the cross-endpoint risk of bias of the ASCENT study as high, as 3.6% of patients in the intervention arm and 14.3% in the control arm did not receive study medication after randomisation and it was unclear how these patients were taken into account in the evaluation for the endpoint of overall survival. For the other endpoints of morbidity and quality of life, it is clear from the dossier of the pharmaceutical company that the subjects who did not receive any study medication were not considered in the evaluations.

In the written statement procedure, the pharmaceutical company submitted information on the reasons for the study discontinuation, the observation status, as well as the duration of observation and censoring for overall survival. This information shows that no patients in the intervention arm and 8 (3.6%) patients in the control arm were censored at the time of randomisation.

Taking into account the small number of subjects censored for overall survival at the time of randomisation, the risk of bias at study level and for the endpoint of overall survival is rated as low.

For the results of the endpoints of symptomatology and health-related quality of life, the risk of bias is classified as high due to the non-inclusion of subjects who did not receive any study medication, as well as due to the open-label study design with subjective endpoint survey and the decreasing return rate for the questionnaire in the course of the study.

The results for the endpoint of discontinuation due to AEs are assesses as having a high risk of bias due to the subjective decision to discontinue therapy. In addition, there is a high risk of bias for the specific AE due to the lack of blinding.

In summary, the G-BA derives an indication for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Trodelvy with the active ingredient sacituzumab govitecan.

Sacituzumab govitecan is approved for the treatment of adults with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one for advanced disease.

The assessment is based on the open-label, randomised, multicentre phase III ASCENT study, which investigated sacituzumab govitecan in comparison with chemotherapy of the doctor's choice with the treatment options capecitabine, vinorelbine, eribulin or gemcitabine (each as monotherapy).

The assessment is based on evaluations of a sub-population of study participants for whom capecitabine, vinorelbine or eribulin was selected as the active ingredient to be administered in the control arm prior to randomisation.

The G-BA determined capecitabine or eribulin or vinorelbine or anthracycline or taxane-containing therapy as the appropriate comparator therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment).

For the endpoint of overall survival, there is a statistically significant difference to the advantage of sacituzumab govitecan compared to capecitabine, eribulin or vinorelbine. The magnitude of the effect is assessed as a very significant improvement.

With regard to symptomatology, the EORTC QLQ-C30 shows several advantages and one disadvantage for sacituzumab govitecan compared with the comparator therapy.

With regard to quality of life, the EORTC QLQ-C30 shows only positive effects of sacituzumab govitecan compared to the appropriate comparator therapy.

For the side effects, there is an advantage of sacituzumab govitecan in serious AEs and, in detail, advantages and disadvantages in specific AEs, with the positive effects of sacituzumab govitecan predominating.

In the overall assessment, a major additional benefit is identified for sacituzumab govitecan.

The reliability of data for the identified additional benefit is classified as an indication.

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 G-BA bases its resolution on the information from the dossier of the pharmaceutical company. However, the following uncertainties arise:

The dossier includes estimates of survival times, which in combination with the percentage values presented in the dossier for triple-negative breast cancer lead to an underestimation. This does not take into account patients who enter the unresectable non-metastatic stage by 2021 and could still be assessed in 2021.

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 Trodelvy (active ingredient: sacituzumab govitecan) at the following publicly accessible link (last access: 13 April 2022):

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

Treatment with sacituzumab govitecan should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in obstetrics and gynaecology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of adults with breast cancer.

It must be administered in an environment where full resuscitation equipment is immediately available.

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 May 2022).

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

Treatment period:

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Sacituzumab govitecan	1 x on day 1 and 8 of a 21-day cycle	17.4	2	34.8

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Capecitabine	2 x on day 1 - 14 of a 21-day cycle	17.4	14	243.6
Vinorelbine	1 x every 7 days	52.1	1	52.1
Eribulin	1 x on day 1 and 8 of a 21-day cycle	17.4	2	34.8

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Anthracycline or taxane-containing therapy				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Doxorubicin	1 x per 21-day cycle	5 - 11[2]	1	5 - 11
Doxorubicin, pegylated	1 x per 28-day cycle	13.0	1	13.0
Epirubicin	1 x per 21-day cycle	6 - 8 [3]	1	6 - 8
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Nab-paclitaxel	1 x per 21-day cycle	17.4	1	17.4

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.

[2] Based on total cumulative dose of maximum 450 - 550 mg/m².

[3] According to the product information of epirubicin, a total cumulative dose of the active ingredient of 900 - 1,000 mg/m² should not be exceeded.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The average body measurements of adult females were applied for dosages, depending on body surface area (BSA) (average body height: 1,66 m; average body weight: 68.7 kg). This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).[4]

For doxorubicin and epirubicin, the total cumulative dose was considered (450 - 550 mg/m² for doxorubicin or 900 - 1,000 mg/m² for epirubicin). Product information with different dosage recommendations is available for doxorubicin and epirubicin (doxorubicin: 50 - 80 mg/m² and 60 - 75 mg/m²; epirubicin: 75 - 90 mg/m² and 60 - 90 mg/m². The dosage recommendations with the largest range were used for the cost calculation: Doxorubicin 50 - 80 mg/m² and epirubicin: 60 - 90 mg/m². In the table "Consumption", only the dosing schemes that result in the range of annual treatment costs when calculated are shown.

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					
Sacituzumab govitecan	10 mg/kg = 687 mg	687 mg	4 x 200 mg	34.8	139.2 x 200 mg
Appropriate comparator therapy					
Capecitabine	2,150 mg[5]	4,300 mg	8 x 500 mg + 2 x 150 mg	243.6	1,948.8 x 500 mg + 487.2 x 150 mg
Vinorelbine	25 - 30 mg/m² = 44 mg - 52.8 mg	44 mg - 52.8 mg	1 x 50 mg – 1 x 50 mg + 1 x 10 mg	52.1	52.1 x 50 mg - 52.1 x 50 mg + 52.1 x 10 mg
Eribulin	1.23 mg/m² = 2.16 mg	2.16 mg	3 x 0.88 mg	34.8	104.4 x 0.88 mg
Anthracycline or taxane-containing therapy					
Docetaxel	100 mg/m² = 176 mg	176 mg	1 x 160 mg + 1 x 20 mg	17.4	17.4 x 160 mg + 17.4 x 20 mg

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[5] Product information of capecitabine (Xeloda®): Standard dosage for BSA 1.67-1.78: 2,150 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
Doxorubicin	50 mg/m² - 80 mg/m² = 88 mg - 140.8 mg -	88 mg - 140.8 mg	1 x 100 mg – 1 x 150 mg	5 - 11	5 x 100 mg - 11 x 150 mg
Doxorubicin, pegylated	50 mg/m² = 88 mg	88 mg	2 x 20 mg + 1 x 50 mg	13.0	26.0 x 20 mg + 13.0 x 50 mg
Epirubicin	60 mg/m² - 90 mg/m² = 105.6 mg - 158.4 mg	105.6 mg - 158.4 mg	1 x 100 mg + 1 x 10 mg - 1 x 100 mg + 1 x 50 mg + 1 x 10 mg	6 - 8	6 x 100 mg + 6 x 10 mg - 8 x 100 mg + 8 x 50 mg + 8 x 10 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Nab-paclitaxel	260 mg/m2 = 457.6 mg	457.6 mg	5 x 100 mg	17.4	87 x 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 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 the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Sacituzumab govitecan 200 mg	1 PCI	€ 1,273.06	€ 1.77	€ 69.86	€ 1,201.43
Appropriate comparator therapy					
Capecitabine 150 mg[6]	120 FCT	€ 54.11	€ 1.77	€ 3.39	€ 48.95
Capecitabine 500 mg[6]	120 FCT	€ 151.81	€ 1.77	€ 11.11	€ 138.93
Docetaxel 20 mg	1 CIS	€ 154.13	€ 1.77	€ 6.78	€ 145.58
Docetaxel 160 mg	1 CIS	€ 1,160.06	€ 1.77	€ 54.52	€ 1,103.77
Doxorubicin 100 mg[6]	1 SFI	€ 285.75	€ 1.77	€ 21.71	€ 262.27
Doxorubicin 150 mg[6]	1 CIS	€ 418.32	€ 1.77	€ 32.19	€ 384.36
Doxorubicin, pegylated 20 mg	1 CIS	€ 776.63	€ 1.77	€ 42.37	€ 732.49
Doxorubicin, pegylated 50 mg	1 CIS	€ 1,912.60	€ 1.77	€ 105.94	€ 1,804.89
Epirubicin 10 mg	1 CIS	€ 39.47	€ 1.77	€ 1.34	€ 36.36
Epirubicin 50 mg	1 CIS	€ 155.41	€ 1.77	€ 6.84	€ 146.80
Epirubicin 100 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Eribulin 0.88 mg	6 SFI	€ 2,429.93	€ 1.77	€ 135.48	€ 2,292.68
Paclitaxel 30 mg	1 CIS	€ 115.75	€ 1.77	€ 4.96	€ 109.02
Paclitaxel 300 mg	1 CIS	€ 891.24	€ 1.77	€ 41.76	€ 847.71
nab-paclitaxel 100 mg	1 PIS	€ 429.33	€ 1.77	€ 52.91	€ 374.65
Vinorelbine 10 mg	10 CIS	€ 293.98	€ 1.77	€ 13.42	€ 278.79
Vinorelbine 50 ng	10 CIS	€ 1,424.53	€ 1.77	€ 67.07	€ 1,355.69
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for infusion; PIS = powder for the preparation of an infusion suspension; PCI = powder for a concentrate for the preparation of a solution for infusion					

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Costs for additionally required SHI services:

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

[6] Fixed reimbursement rate

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.

Designation of the therapy	Packaging size	Cost (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Dexamethasone[6] 2 x 20 mg	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	17.4	€ 81.49
Dimetindene IV 1 mg/10 kg = 6.87 mg	5 SFI (4 mg)	€ 18.86	€ 1.77	€ 1.90	€ 15.19	17.4	€ 105.72
Cimetidine IV 300 mg	10 AMP	€ 19.77	€ 1.77	€ 0.40	€ 17.60	17.4	€ 61.25

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 drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies 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 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

At its session on 7 April 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 November 2021, the pharmaceutical company submitted a dossier for the benefit assessment of sacituzumab govitecan to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 December 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient sacituzumab govitecan.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 12 April 2022.

By letter dated 12 April 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 29 April 2022.

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 was discussed at the session of the subcommittee on 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 April 2021	Determination of the appropriate comparator therapy
Working group Section 35a	6 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	12 April 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	21 April 2022 4 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

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

Prof. Hecken