Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V atezolizumab (Reassessment Based on New Scientific Knowledge: Urothelial Carcinoma)

From 20 June 2019

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient atezolizumab as an active ingredient of the medicinal product Tecentriq® was first placed on the (German) market on 2 October 2017. The G-BA prompted a new benefit assessment in accordance with 35a, paragraph 1 SGB V in conjunction with Section 3, paragraph 1 no. 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and Chapter 5, Section 13 Rules of Procedure (VerfO) for the active ingredient atezolizumab at the request of its members in the resolution of 2 August 2018. The new benefit assessment was initiated on the basis of new scientific findings from the current IMvigor130 (NCT02807636) study and a related change in the approved therapeutic indication of atezolizumab by resolution of the EU Commission dated 2 July 2018.

The relevant date for the first placing on the market of the active ingredient atezolizumab in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is 02 January 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 6 VerfO. on 19 December 2018.

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 01 April 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of atezolizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier evaluation prepared by the IQWiG, and the statements submitted in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA 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 atezolizumab.

In 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 atezolizumab (Tecentriq®) in accordance with the product information

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC)

- after prior platinum-based chemotherapy or
- who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%.

2.1.2 Appropriate comparator therapy

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

a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

Chemotherapy according to the doctor's instructions

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 practice unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the efficiency principle.

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, in principle, have a marketing authorisation for the therapeutic indication.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

2. If a non-medical treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-drug 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 addition to atezolizumab, the active ingredients doxorubicin, methotrexate, and pembrolizumab are authorised for the first-line treatment of urothelial carcinoma in patients not eligible for cisplatin.

On 2. Non-drug treatment is not indicated in this therapeutic situation.

On 3. The following resolutions and guidelines of the G-BA have been issued on drug therapies in the present therapeutic indication:

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

Atezolizumab: Resolution of 16 March 2018

Pembrolizumab: Resolution of 16 March 2018

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

The guidelines unanimously recommend cisplatin in combination with gemcitabine for first-line treatment of advanced metastatic urothelial carcinoma.

However, a relevant number of patients are not eligible for cisplatin-containing chemotherapy. However, the combination therapy of carboplatin and gemcitabine recommended by the guidelines for this patient population in particular is not authorised for this therapeutic indication. However, patients who are unsuitable for cisplatin should not be considered clinically as a uniform group. For patients with poor general condition, for example, monochemotherapy is mentioned in the guidelines as an alternative to carboplatin with gemcitabin. However, in the written statements of medical experts in the present benefit assessment procedure, treatment with monochemotherapy, in particular with the active ingredients methotrexate and doxorubicin, was not given any relevant significance in the reality of care.

The PD-1 antibody pembrolizumab is another treatment option authorised in the present therapeutic indication. Because it is still quite new in the field of care, the therapeutic significance cannot yet be conclusively assessed. By resolution of 16 March 2018, no additional benefit could be identified for pembrolizumab. The active ingredient is currently being subjected to a further benefit assessment procedure. Pembrolizumab is not currently being considered as an appropriate comparator therapy.

Against this background, the G-BA has identified chemotherapy according to the doctor's instructions as an appropriate comparator therapy for the sub-population of patients who are not eligible for a cisplatin-containing chemotherapy. The active ingredients discussed in the above justification shall be taken into account.

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

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven for the treatment of locally advanced or metastatic urothelial carcinoma in adult patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5%.

Justification:

In the dossier, the pharmaceutical company shall not present any results from directly comparative studies or studies suitable for an adjusted indirect comparison.

In order to demonstrate the additional benefit of atezolizumab compared to the appropriate comparator therapy, the pharmaceutical company compares the results of single-arm studies or of individual arms of comparative studies in this partial therapeutic indication (non-adjusted). The results presented correspond as far as possible to the data submitted by the pharmaceutical company within the framework of the initial evaluation of the originally approved therapeutic indication of atezolizumab.

Comparative results from the ongoing, partially blinded, controlled, and randomised Imvigor130 Phase III study, which, in a three-armed design, compares atezolizumab monotherapy with a combination therapy of atezolizumab with gemcitabine plus cisplatin or carboplatin as well as a combination therapy of placebo with gemcitabine plus cisplatin or carboplatin, are not yet available. This study included adult patients with locally advanced or metastatic urothelial carcinoma who had not been pretreated in this disease stage. The restriction on authorisation of atezolizumab resulted from an unplanned analysis of the IMvigor130 study as part of the regular review by an Independent Data Monitoring Committee (IDMC), which showed reduced survival in patients with low PD-L1 expression under atezolizumab compared to standard chemotherapy.

For atezolizumab, the results of the multi-centre, open, single-arm IMvigor210 study are thus available as for the initial evaluation. A total of 123 patients without prior chemotherapy for the treatment of inoperable, locally advanced, or metastatic urothelial carcinoma were included in the evaluation-relevant cohort of the study. Treatment with atezolizumab (with a dosage that complied with summary of product characteristics) was continued until disease progression, the occurrence of unacceptable toxicities, or a change in therapy. The primary endpoint was the objective response rate according to RECIST criteria. Secondary endpoints were response duration, progression-free survival, and overall survival. Results on morbidity endpoints and health-related quality of life are not available. Adverse events, both in terms of relevant overall rates and specific chemotherapy-associated and immunotherapy-associated events, were also reported for the benefit assessment dossier.
In addition to the results submitted during the initial evaluation, an additional, more recent IMvigor210 data cut-off (12 July 2017) was evaluated for this assessment.

The pharmaceutical company uses the combination carboplatin and gemcitabine as the sole comparator therapy and has identified corresponding studies in which the patients received this combination. Four of the studies used were one-armed (Bellmunt 2001, Carles 2000, Linardou 2004, and Bamias 2007). A single study arm of the 2012 De Santis study was also included.

Against the background of the special situation of medical treatment and provision of medical care in the therapeutic indication described above, the G-BA sees a factual medical reason that exceptionally justifies taking into account the data from the indirect comparison with carboplatin and gemcitabine.

If the combination of carboplatin and gemcitabine used as comparator in the studies has not been used in compliance with the authorisation, it is not possible to draw any conclusions about their usefulness in the application form exceeding authorisation in the standard care of

insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V.

The ineligibility for cisplatin-based therapy was operationalised as the presence of at least one criterion according to Galsky 2011: reduced general condition (ECOG ≥ 2 or Karnofsky index 60 to 70%), impaired renal function, hearing loss or peripheral neuropathy (CTCAE ≥ 2 in each case), or heart failure with NYHA severity of III). This is in line with the criteria used in the IMvigor210 study to determine that cisplatin is not a suitable treatment option.
Different endpoints were reported in the publications on the studies. Results on overall survival are available from only four studies; results on the endpoint categories morbidity and quality of life are completely absent. As already described in the initial assessment, the data basis with regard to adverse events is again incomplete because no comparative data are available for some adverse events.

As in the dossier for the initial evaluation, the basis for the present comparison is the respective overall populations of the studies in accordance with the originally approved therapeutic indication of atezolizumab. However, the relevant sub-population of patients with tumours showing PD-L1 expression ≥ 5% from the IMvigor210 study would have been decisive. For these, the pharmaceutical company presents the results only descriptively. The patient population in accordance with the restriction on authorisation included 32 of the 123 patients included in the study.

Overall assessment

The data provided by the pharmaceutical company are not suitable to be able to derive an additional benefit of atezolizumab compared to the appropriate comparator therapy. On one hand, the data are incomplete, particularly with regard to adverse events. Because of this incomplete data basis, no proper comparison of atezolizumab with the appropriate comparator therapy can be made. On the other hand, the effects presented are not large enough to exclude that the differences are not solely due to disturbances.

Taking into account the current data cut-off (12 July 2017), the median overall survival in the single-arm IMvigor210 study (16.3 months) compared with results under gemcitabine and carboplatin treatment (7.2 to 10 months) is marginally longer than at the data cut-off available at the time of initial assessment. In addition, it should be noted that for the sub-population with tumours with PD-L1 expression ≥ 5% (population in accordance with current marketing authorisation), the median overall survival is only 12.3 months.
Within the framework of the four individual comparisons of overall survival carried out by the pharmaceutical company, only the results of two evaluations are statistically significantly different also for the current data cut-off.

Because of the high uncertainty of the results, statements on the additional benefit based on a comparison of individual arms of different studies can be made only if very large effects are present. However, such effects are not present for relevant endpoints on overall survival, symptoms, health-related quality of life, and adverse events.

In summary, no suitable data are available to derive an additional benefit from atezolizumab as monotherapy. This applies in particular to the patient population in accordance with the current marketing authorisation (patients with tumours with a PD-L1 expression ≥ 5%). Therefore, for patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5%, an additional benefit of atezolizumab as monotherapy is not proven because of the limited data basis.

2.1.4 Limitation of the period of validity of the resolution

a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

The limitation of the period of validity of the resolution on the benefit assessment of atezolizumab has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a, paragraph 1 SGB V.

The results of the currently ongoing IMvigor130 study, on the basis of which the EMA[2] modified the present approved therapeutic indication for atezolizumab, are not yet available. In view of the fact that clinical data on patient-relevant endpoints, especially on overall survival relevant for the benefit assessment of the drug are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the additional benefit of atezolizumab is available. The limitation will permit the upcoming results from the IMvigor130 study to be promptly incorporated into the benefit assessment of the drug in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 01/10/2021 to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the study results for all patient-relevant endpoints from the current IMvigor130 study should be included in the dossier.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, No. 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the drug atezolizumab shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of atezolizumab in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

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

2.1.5 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient atezolizumab on the basis of an application based on new scientific findings according to Section 13 (Chapter 5, Section 13, paragraph 1, sentence 1 VerfO).

The renewed benefit assessment refers exclusively to the use of atezolizumab as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in the following patient groups:

[2] European Medicines Agency

a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

About patient group a)

The appropriate comparator therapy for atezolizumab as monotherapy was determined by the G-BA as follows:

Chemotherapy according to the doctor's instructions

For this patient group, the pharmaceutical company presents the results of the IMvigor210 single-arm study on the treatment with atezolizumab in patients with advanced or metastatic urothelial carcinoma. In a non-adjusted comparison, these are compared with the results of studies on combination therapy with carboplatin and gemcitabine.

Against the background of the special situation of medical treatment and provision of medical care in the therapeutic indication, the G-BA sees a factual medical reason that exceptionally justifies taking into account the data from the indirect comparison with carboplatin and gemcitabine.

No conclusions can be drawn from this as to the usefulness of the combination of carboplatin and gemcitabine in the application form exceeding authorisation in the standard care of insured persons in the SHI system.

The basis for the present comparison is the respective overall populations of the studies in accordance with the originally approved therapeutic indication of atezolizumab without restriction with regard to PD-L1 expression. For the IMvigor210 study, a more recent data cut-off compared to the initial assessment of atezolizumab was taken into account.

The data provided by the pharmaceutical company were not suitable to be able to derive an additional benefit of atezolizumab compared to the appropriate comparator therapy because the data basis was incomplete, particularly with regard to undesirable events. In addition, the effects presented were not large enough to exclude that the differences were not solely due to disturbances. Furthermore, for the present comparison, the relevant sub-population of patients with tumours showing PD-L1 expression ≥ 5% from the IMvigor210 study would have been decisive. However, results for these patients were presented only descriptively. Therefore, no suitable data are available in particular for this patient population in accordance with the current marketing authorisation.

Overall, for patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5%, an additional benefit of atezolizumab as monotherapy is not proven because of the limited data basis.

The resolution is limited until 1 October 2021. The results of the currently ongoing IMvigor130 study, on the basis of which the EMA[3] modified the present approved therapeutic indication for atezolizumab, are not yet available. For the renewed benefit assessment after the deadline, the study results for all patient-relevant endpoints from the currently ongoing IMvigor130 study should be included in the dossier.

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 information from the dossier of the pharmaceutical company for patients ineligible for cisplatin whose tumours show PD-L1 expression ≥ 5%. These refer to the derivation of the target population used in the resolution on the benefit assessment of

[3] European Medicines Agency

atezolizumab (resolution of 16 March 2018) and also take into account a corresponding proportion of patients with tumours with PD-L1 expression ≥ 5%.

The derivation of patient numbers is comprehensible in principle; however, is also fraught with uncertainties that tend to lead to underestimation. There are uncertainties, in particular with regard to the proportion of patients who are not eligible for cisplatin-containing therapy. In the American registry study on which the data were based, only patients diagnosed with bladder carcinoma were considered. Urothelial carcinomas of other urinary organs were not considered. Even more relevant, however, was the fact that only patients with impaired renal function were considered ineligible for cisplatin therapy and were therefore included in the registry study. Further contraindications for cisplatin-containing therapy such as the presence of peripheral neuropathy, existing hearing damage and, in particular, heart failure, were not considered.

Furthermore, there are uncertainties with regard to the proportion of patients with tumours with a PD-L1 expression ≥ 5% because the proportional value used refers exclusively to the single-arm pivotal study of atezolizumab and is therefore subject to uncertainty because of the selectivity of the study populations.

Overall, for the reasons mentioned, it can be assumed that the numbers of patients ineligible for cisplatin whose tumours show a PD-L1 expression of ≥ 5% are higher than those determined by the pharmaceutical company. There is therefore a potential underestimation. Notwithstanding this, the patient numbers thus determined represent the best estimate currently available.

2.3 Requirements for a quality-assured application

The requirements of 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 Tecentriq® (active ingredient: atezolizumab) at the following publicly accessible link (last access: 02 May 2019):

https://www.ema.europa.eu/documents/product-information/tecentriq-epar-product-information_de.pdf

Only specialists in internal medicine, haematology, and oncology with experience treating patients with urothelial carcinoma, specialists in urology, and specialists participating in the Oncology Agreement may initiate and monitor treatment with atezolizumab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material and a patient card. Patients are requested to carry their patient cards with them at all times. The training material for health professionals and the patient card shall include, in particular, instructions on how to deal with the potential immune-mediated adverse reactions to atezolizumab as well as infusion reactions.

2.4 Treatment costs

The treatment costs are based on the contents of the summary of product characteristics and the information listed in the LAUER-TAXE® (last revised: 1 June 2019).

If no maximum therapy duration is specified in the summary of product characteristics, the treatment duration is assumed to be one year, even if the actual therapy duration is patient-individualized and/or is shorter on average.

Costs of the appropriate comparator therapy

The evidence for therapeutic options in the treatment of patients not eligible for cisplatin is limited overall. In the guidelines that explicitly recommend chemotherapy for these patients, the combination of carboplatin with gemcitabine is recommended. This combination is not authorised for the present indication. For patients with poor general condition, for example, monochemotherapy is mentioned as an alternative. However, in the written statements of medical experts in the present benefit assessment procedure, this was not given any relevant significance in the reality of care. Chemotherapy takes place according to the doctor's instructions. The active ingredients discussed in the justification of the appropriate comparator therapy must be taken into account.

Against this background, the G-BA considers it inappropriate to reflect the treatment costs on the basis of the costs for individual therapy options and notes that the treatment costs are patient-individualized.

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				
Atezolizumab	continuously, every 3 weeks	17	1	17
Appropriate comparator therapy				
Patient population a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)				
Chemotherapy according to the doctor's instructions	patient-individualized			

Usage and consumption:

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/year	Average annual consumption by potency
Medicinal product to be assessed					
Atezolizumab	1,200 mg	1,200 mg	1 × 1,200 mg	17	17 × 1,200 mg
Appropriate comparator therapy					

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Patient population a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)					
Chemotherapy according to the doctor's instructions	patient-individualized				

Costs:

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less statutory rebates in accordance with Sections 130 and 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 pharmaceutical costs were then calculated on the basis of the costs per pack less 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					
Atezolizumab	1 IFK	€ 4,691.99	€ 1.77	€ 264.69	€ 4,425.53
Appropriate comparator therapy					
Chemotherapy according to the doctor's instructions	patient-individualized				
Abbreviations. IFC = Concentrate for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 June 2019

Costs for additionally required SHI services:

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

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

Because there are no regular differences in the necessary 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, no costs for

additional SHI services required had to be taken into account.

Other services covered by SHI funds:

The auxiliary tax (contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

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

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its meeting on 15 August 2017.

Because of new scientific findings, the appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redetermined the appropriate comparator therapy at its meeting on 25 September 2018 .

On 19 December 2018, the pharmaceutical company submitted a dossier for the benefit assessment of atezolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 19 December 2018 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 atezolizumab .

The dossier assessment by the IQWiG was submitted to the G-BA on 27 March 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 01 April 2019. The deadline for submitting written statements was 23 April 2019.

The oral hearing was held on 6 May 2019.

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

The evaluation of the written statements received and the oral hearing was discussed at the meeting of the subcommittee on 12 June 2019, and the proposed resolution was approved.

At its meeting on 20 June 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	15 August 2017	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	25 September 2018	Redefinition of the appropriate comparator therapy
Working group Section 35a	29 April 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2019	Conduct of the oral hearing
Working group Section 35a	14 May 2019 21 May 2019 4 June 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal products	12 June 2019	Concluding discussion of the proposed resolution
Plenum	20 June 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 June 2019

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

Prof. Hecken