Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee on an amendment to the Pharmaceuticals Directive
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Nivolumab (new therapeutic indication: urothelial carcinoma, PD-L1 expression ≥ 1%, adjuvant treatment)

of 16 March 2023

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.

According to Section 35a paragraph 6 SGB V, the G-BA can also initiate a benefit assessment according to Section 35a paragraph 1 SGB V for reimbursable medicinal products with an active ingredient that is not a new active ingredient according to Section 35a paragraph 1 SGB V, if a new marketing authorisation with new dossier protection is granted for the medicinal product. 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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

At its session on 20 October 2022, the G-BA decided on the benefit assessment of nivolumab in accordance with Section 35a SGB V. Following the publication of the resolution on the G-BA's website, the G-BA came to the conclusion that there was a need to adjust the information in the resolution with regard to the table of results on side effects and the treatment costs presented in the resolution.

On point 1 Table of results "Side effects"

Following the publication of the resolution on the G-BA's website, the G-BA determined that in the resolution on the benefit assessment of nivolumab of 20 October 2022, an incorrect statement of the results on side effects for the endpoint "severe adverse events (CTCAE grade ≥ 3)" was made in the column "nivolumab" in the table of results of the CA209-274 study. The information "0.84 [0.58; 1.23]; 0.380" shall be replaced with "9.49 [6.11; 13.80] 74 (53.2)".

On point 4 "Treatment costs"

Furthermore, following the publication of the resolution on the G-BA's website, the G-BA came to the conclusion that there is a need for an adjustment of the information on the treatment costs presented in the resolution.

According to the product information, therapy with nivolumab in the therapeutic indication under assessment may last a maximum of 1 year.

In the resolution of 20 October 2022, 26.1 treatment days per patient per year were used as the basis for calculating the annual treatment costs of nivolumab. The review of the resolution of 20 October 2022 showed that, due to the maximum treatment duration, only the completed cycles in the treatment year and thus, 26 treatment days per patient are to be used as the basis for calculating the annual treatment costs of nivolumab and consequently there is an overestimation of the annual treatment costs.

Furthermore, in the resolution of 20 October 2022, the publication by Lehmann et al.[1] was used to calculate the annual treatment costs of cisplatin in combination with methotrexate against the background of the lack of information on the dosage as well as the treatment duration in the respective product information. Based on the publication, a treatment duration of 3 cycles was used for cisplatin in combination with methotrexate. The review of the resolution of 20 October 2022 showed that, against the background of the missing information on the treatment duration in the product information, one year (365 days) is to be assumed mathematically with regard to the treatment duration and consequently there is an underestimation of the annual treatment costs.

The annual treatment costs for nivolumab and cisplatin in combination with methotrexate are adjusted using the following treatment duration, consumption and costs.

<u>Treatment period:</u>

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 varies 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.

Based on the specifications in the product information, the treatment duration for adjuvant treatment with nivolumab is limited to 12 months, but may be shorter on a patient-individual basis. Against this background, therefore, only the completed cycles in the treatment year are considered for nivolumab.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nivolumab	1 x per 14-day cycle	26.1	1	26
	or			
	1 x per 28-day cycle	13.0	1	13
Appropriate comparator therapy				
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment				
Cisplatin in combination with gemcitabine				
Cisplatin	1x on day 1 or day 2 per 28-day cycle	13.0	1	13
Gemcitabine	1x on day 1, 8 and 15 per 28-day cycle	13.0	3	39
Cisplatin in combination with methotrexate				
Cisplatin	1x on day 1 per 21-day cycle	17.4	1	17.4
Methotrexate	1x on day 8 and 15 of a 21-day cycle	17.4	2	34.8
b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment				
Monitoring wait-and-see approach	incalculable			

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

The (daily) doses recommended in the product information or in the labelled publication were used as the basis for calculation.

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					
Nivolumab	240 mg	240 mg	2 x 120 mg	26	52.0 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	13	52.0 x 120 mg
Appropriate comparator therapy					
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment					
Cisplatin in combination with gemcitabine					
Cisplatin	70 mg/m² BSA = 133 mg	133 mg	1 x 100 mg 1 x 50 mg	13	13 x 100 mg 13 x 50 mg
Gemcitabine	1,000 mg/m² BSA = 1,900 mg	1,900 mg	2 x 1,000 mg	39	78 x 1,000 mg
Cisplatin in combination with methotrexate[1]					
Cisplatin	70 mg/m² BSA = 133 mg	133 mg	1 x 100 mg 1 x 50 mg	17.4	17.4 x 100 mg 17.4 x 50 mg
Methotrexate	40 mg/m² BSA = 76 mg	76 mg	2 x 50 mg	34.8	69.6 x 50 mg
b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment					
Monitoring wait-and-see approach	incalculable				

[1] Lehmann J, Retz M, Wiemers C, Beck J, Thüroff J, Weining C, et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomised, multicentre, phase III trial (AUO-AB 05/95). J Clin Oncol 2005;23:4963-4974.

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					
Nivolumab 120 mg	12 ml CIS	€ 1,546.93	€ 1.77	€ 85.05	€ 1,460.11
Appropriate comparator therapy					
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment					
Cisplatin in combination with gemcitabine					
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Gemcitabine 1000 mg	1000 mg PIS	€ 102.32	€ 1.77	€ 10.62	€ 89.93
Cisplatin in combination with methotrexate					
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Methotrexate[2] 50 mg	2 ml SFI	€ 49.14	€ 1.77	€ 2.99	€ 44.38
b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment					
Monitoring wait-and-see approach	incalculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIS = powder for the preparation of an infusion solution					

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[2] Fixed reimbursement rate

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.

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	Treatment days/ year	Cost/ patient/ year
Appropriate comparator therapy							
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy, adjuvant treatment							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Cisplatin in combination with gemcitabine							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	13	€ 118.43
Sodium chloride 0.9% Inf. Solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	13	€ 124.29 - € 192.88
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Cisplatin in combination with methotrexate							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	17.4	€ 166.36 - € 258.16

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	Treatment days/ year	Cost/ patient/ year
Sodium chloride 0.9% Inf. Solution, 3 l - 4.4 l/day	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Abbreviation: INF = infusion solution							

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3. Written statement procedure according to Section 92, paragraph 3a SGB V

The amendment of the Pharmaceuticals Directive does not require the implementation of a written statement procedure according to Section 92, paragraph 3a SGB V. Pharmaceutical companies are not adversely affected by the correction of the information; the amendment merely corrects the presentation in the table of results on "severe adverse events (CTCAE grade ≥ 3)" of the study. However, this does not entail any significant changes to the content of the resolution, so that no new written statement procedure needs to be carried out.

In addition, pharmaceutical companies are not adversely affected by the correction of the information on the costs of the active ingredient nivolumab as well as the active ingredient cisplatin in combination with methotrexate; with the amendment, only a factual and arithmetical correction of the cost representation is made.

4. 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.

5. Process sequence

After the adoption of the resolution, the necessity of adjusting the information in the resolution with regard to the table of results as well as the calculation of the annual treatment costs of nivolumab as well as the appropriate comparator therapy by resolution of 20 October 2022 on an amendment to the Pharmaceuticals Directive Annex XII - Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V - nivolumab came to light.

The issue was discussed in the working group Section 35a and in the Subcommittee on Medicinal Products.

At its session on 16 March 2023, the plenum resolved by consensus to amend the AM-RL with regard to an adjustment of the information in the resolution concerning the table of results as well as the cost representation in the resolution of 20 October 2022.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	17 January 2023 31 January 2023 14 February 2023	Consultation on the issue
Subcommittee Medicinal products	7 March 2023	Consultation on an amending resolution regarding the table of results on side effects as well as the cost representation of the resolution of 20 October 2022
Plenum	16 March 2023	Drafting of resolution on an amending resolution with regard to the table of results on side effects as well as the cost representation of the resolution of 20 October 2022

Berlin, 16 March 2023

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

Prof. Hecken