Nivolumab (new therapeutic indication: Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, CPS ≥ 5, HER2-negative, first-line, combination with fluoropyrimidine- and platinum-based combination chemotherapy)

Valid until: unlimited

Resolution of: 19 May 2022/12. July 2022
Entry into force on: 19 May 2022/12. July 2022
Federal Gazette, BAnz AT 27 06 2022 B2/ BAnz AT 05 08 2022 B3

New therapeutic indication (according to the marketing authorisation of 19 October 2021):

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

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

See new therapeutic indication according to marketing authorisation.

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

Adults with locally advanced or metastatic HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma which cannot be treated curatively and whose tumours express PD-L1 (combined positive score (CPS) ≥ 5); first-line therapy

Appropriate comparator therapy:

- Therapy according to doctor's instructions

Extent and probability of the additional benefit of Nivolumab in combination with FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) compared to FOLFOX or XELOX:

Hint of a considerable additional benefit

Study results according to endpoints:

Adults with locally advanced or metastatic HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma which cannot be treated curatively and whose tumours express PD-L1 (combined positive score (CPS) ≥ 5); first-line therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	n.a.	There are no usable data for the benefit assessment
Health-related quality of life	↑	Advantage in the FACT-Ga endpoint
Side effects	↓	Disadvantages in the endpoint discontinuation due to AEs as well as in detail with specific AEs

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

CheckMate 649 study:[1,2]

- randomised, controlled, open study
- Nivolumab in combination with FOLFOX (5-FU + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) **vs** FOLFOX or XELOX
- Relevant sub-population: PD-L1-positive population (patients with CPS ≥ 5; 60.4 % of the total study population)

[1] Data from the dossier assessment of the IQWiG (A21-146) and from the addendum (A22-44), unless otherwise indicated.
[2] Data cut-off from 27.05.2021

Mortality

Endpoint	**Nivolumab + chemotherapy (FOLFOX or XELOX)**		**Chemotherapy (FOLFOX or XELOX)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	473	14.39 [13.08; 16.23] *363 (76.7)*	482	11.10 [10.02; 12.09] *416 (86.3)*	0.70 [0.61; 0.81] < 0.001 3.29 months

Morbidity

Endpoint	**Nivolumab + chemotherapy (FOLFOX or XELOX)**		**Chemotherapy (FOLFOX or XELOX)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	473	7.69 [7.03; 9.17] *328 (69.3)*	482	6.05 [5.55; 6.90] *350 (72.6)*	0.68 [0.56; 0.81] <0.0001 1.64 months
Disease symptomatology					
Not assessed					
Health status					
EQ-5D VAS					
No usable data available					

Health-related quality of life

Endpoint	**Nivolumab + chemotherapy (FOLFOX or XELOX)**		**Chemotherapy (FOLFOX or XELOX)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Health-related quality of life - time to first deterioration under treatment[c]					
FACT-Ga (Functional Assessment of Cancer Therapy-Gastric)					
FACT-Ga	387	n.a. *56 (14.5)*	354	n.a. [21.03; n.c.] *69 (19.5)*	0.59 [0.41; 0.84] 0.006
PWB (physical wellbeing)	393	9.79 [7.06; n.c.] *160 (40.7)*	359	7.39 [5.55; 17.77] *144 (40.1)*	0.81 [0.64; 1.02]
SWB (social wellbeing)	393	15.57 [10.91; 38.47] *137 (34.9)*	359	11.07 [7.23; 16.66] *116 (32.3)*	0.79 [0.61; 1.03
EWB (emotional wellbeing)	389	n.a. [16.43; n.c.] *115 (29.6)*	358	15.54 [9.72; n.c.] *100 (27.9)*	0.77 [0.58; 1.02]
FWB (functional wellbeing)	389	22.24 [11.56; n.c.] *134 (34.4)*	358	15.54 [10.28; n.c.] *116 (32.4)*	0.89 [0.69; 1.16]
GaCS (Gastric Cancer Subscale)	No data available[d]				

Side effects

Endpoint	Nivolumab + chemotherapy (FOLFOX or XELOX)		Chemotherapy (FOLFOX or XELOX)		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (AEs) (presented additionally)[e]					
	468	0.13 [0.10; 0.20] *466 (99.6)*	465	0.16 [0.13; 0.20] *453 (97.4)*	-
Serious adverse events (SAE)[e]					
	468	8.74 [7.10; 12.29] *255 (54.5)*	465	11.04 [9.20; 19.09] *206 (44.3)*	1.17 [0.97; 1.41] 0.107
Severe adverse events (CTCAE grade ≥ 3) [e]					
	468	2.79 [2.43; 3.19] *373 (79.7)*	465	3.25 [2.76; 3.71] *327 (70.3)*	1.10 [0.95; 1.28] 0.194
Discontinuation due to AEs[e, f]					
	468	7.75 [6.74; 10.51] *234 (50.0)*	465	15.18 [9.49; n.c.] *157 (33.8)*	1.39 [1.13; 1.71] 0.002 7.43 months
Specific adverse events					
Immune-mediated AEs[g] (presented additionally)	468	1.48 [1.38; 1.74] *376 (80.3)*	465	2.89 [2.10; 4.01] *285 (61.3)*	-
Immune-mediated SAEs[g]	468	n.a. *63 (13.5)*	465	n.a. *24 (5.2)*	2.59 [1.60; 4.18] < 0.001
Immune-mediated severe AEs[g]	468	n.a. [31.15; n.c.] *114 (24.4)*	465	n.a. *58 (12.5)*	1.81 [1.31; 2.51] < 0.001
Skin and subcutaneous tissue disorders (SOC, AE)	468	12.58 [9.66; n.c.] *202 (43.2)*	465	n.a. *119 (25.6)*	1.67 [1.33; 2.10] < 0.001
Immune system disorders (SOC, AE)	468	n.a. *53 (11.3)*	465	n.a. *20 (4.3)*	2.50 [1.49; 4.18] < 0.001

Endpoint	Nivolumab + chemotherapy (FOLFOX or XELOX)		Chemotherapy (FOLFOX or XELOX)		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Amylase elevated (PT, severe AE)	468	n.a. *14 (3.0)*	465	n.a. *1 (0.2)*	13.01 [1.70; 99.64] 0.001
Peripheral neuropathy (PT, severe AE)	468	n.a. *28 (6.0)*	465	n.a. *10 (2.2)*	2.40 [1.16; 4.94] 0.015

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Data from: European Medicines Agency. Assessment report: Opdivo; data cut-off from 27.05.2020
[c] Time to first deterioration under treatment. A decrease in the score by ≥ 15 % of the scale range compared to start of the study is considered clinically relevant deterioration (scale range FACT-Ga: 0 to 184, PWB: 0 to 28, SWB: 0 to 28, EWB: 0 to 24, FWB: 0 to 28, GaCS: 0 to 76).
[d] The pharmaceutical company does not submit any evaluations over time for this subscale, over which the total score was calculated.
[e] Without detection of progression of the underlying disease
[f] Discontinuation of at least one active ingredient
[g] In each case, the operationalisation of the pharmaceutical company specific MedDRA PT collection from the endpoint "specific adverse events" ("select AEs") is used.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EWB = emotional wellbeing; FACT-Ga = Functional Assessment of Cancer Therapy-Gastric; FOLFOX = 5 fluorouracil + folinic acid + oxaliplatin; FWB = functional well-being; GaCS = Gastric Cancer Subscale; HR = hazard ratio; n.d. = no data available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; PD-L1 = programmed cell death ligand 1; PT = preferred term; PWB = physical wellbeing; RCT = randomised controlled trial; SOC = system organ class; SWB = social well-being; VAS = visual analogue scale; vs = versus; XELOX = capecitabine + oxaliplatin

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with locally advanced or metastatic HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma which cannot be treated curatively and whose tumours express PD-L1 (combined positive score (CPS) ≥ 5); first-line therapy

approx. 500 – 3,100 patients

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 Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 4 March 2022):
https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, internal medicine and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with gastric, gastroesophageal junction or oesophageal carcinoma.

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

4. Treatment costs

Annual treatment costs"[3]:

Adults with locally advanced or metastatic HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma which cannot be treated curatively and whose tumours express PD-L1 (combined positive score (CPS) ≥ 5); first-line therapy

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Nivolumab in combination with 5-fluorouracil and folinic acid and oxaliplatin (FOLFOX-4)	
Nivolumab	€ 76,217.74
5-fluorouracil	€ 1,841.09
Folinic acid	€ 7,908.30
Oxaliplatin	€ 9,894.77
Total	€ 95,861.91
Nivolumab in combination with 5-fluorouracil and folinic acid and oxaliplatin (modified FOLFOX-6)	
Nivolumab	€ 76,217.74
5-fluorouracil	€ 1,171.11
Folinic acid	€ 7,298.87
Oxaliplatin	€ 9,894.77
Total	€ 94,582.49
Nivolumab in combination with capecitabine and oxaliplatin (XELOX)	
Nivolumab	€ 76,217.74
Capecitabine	€ 2,089.64
Oxaliplatin	€ 13,102.90
Total	€ 91,410.28
Appropriate comparator therapy:	
Therapy according to doctor's instructions[4]	
Cisplatin in combination with 5-fluorouracil	
Cisplatin	€ 2,277.14
5-fluorouracil	€ 1,811.34
Total	€ 4,088.48
Additionally required SHI services	€ 328.58 - € 421.62
Cisplatin in combination with 5-fluorouracil and folinic acid	
Cisplatin	€ 2,277.14
5-fluorouracil	€ 1,811.34
Folinic acid	€ 4,865.91
Total	€ 8,954.39
Additionally required SHI services	€ 328.58 - € 421.62

[4] The costs are presented for the active ingredients that are each approved for at least one of the present localisations. The following medicinal product combinations are only approved for the treatment of gastric carcinoma: Cisplatin + capecitabine (XP), oxaliplatin + 5-fluorouracil + folinic acid (FOLFOX-4 and mod. FOLFOX-6), oxaliplatin + 5-fluorouracil + folinic acid (FLO), oxaliplatin + capecitabine (XELOX) , docetaxel + cisplatin + 5-fluorouracil (DCF), docetaxel + oxaliplatin + infusional 5-fluorouracil + folinic acid (FLOT), epirubicin + cisplatin + capecitabine (ECX), epirubicin + oxaliplatin + capecitabine (EOX), epirubicin + cisplatin + 5-fluorouracil (ECF), epirubicin + oxaliplatin + 5-fluorouracil and S-1 (tegafur/ gimeracil/ oteracil) + cisplatin.

Designation of the therapy	Annual treatment costs/ patient
Cisplatin in combination with capecitabine (XP)	
Cisplatin	€ 2,277.14
Capecitabine	€ 2,089.64
Total	€ 4,366.78
Additionally required SHI services	€ 328.58 - € 421.62
Oxaliplatin in combination with 5-fluorouracil and folinic acid (FOLFOX-4)	
Oxaliplatin	€ 9,894.77
5-fluorouracil	€ 1,841.09
Folinic acid	€ 7,908.30
Total	€ 19,644.17
Oxaliplatin in combination with 5-fluorouracil and folinic acid (mod. FOLFOX-6)	
Oxaliplatin	€ 9,894.77
5-fluorouracil	€ 1,171.11
Folinic acid	€ 7,298.87
Total	€ 18,364.74
Oxaliplatin in combination with 5-fluorouracil and folinic acid (FLO)	
Oxaliplatin	€ 9,894.77
5-fluorouracil	€ 793.96
Folinic acid	€ 3,954.15
Total	€ 14,642.88
Oxaliplatin in combination with capecitabine (XELOX)	
Oxaliplatin	€ 13,102.90
Capecitabine	€ 2,089.64
Total	€ 15,192.54
Docetaxel in combination with cisplatin and 5-fluorouracil (DCF)	
Docetaxel	€ 13,742.17
Cisplatin	€ 1,991.08
5-fluorouracil	€ 1,811.34
Total	€ 17,544.59
Docetaxel in combination with oxaliplatin and 5-fluorouracil and folinic acid (FLOT)	
Docetaxel	€ 13,069.58
Oxaliplatin	€ 9,894.77
5-fluorouracil	€ 793.96
Folinic acid	€ 3,954.15
Total	€ 27,712.46
Epirubicin in combination with cisplatin and capecitabine (ECX)	

Designation of the therapy	Annual treatment costs/ patient
Epirubicin	€ 4,964.22
Cisplatin	€ 1,783.85
Capecitabine	€ 2,285.87
Total	€ 9,033.94
Additionally required SHI services	€ 328.58 - € 421.62
Epirubicin in combination with oxaliplatin and capecitabine (EOX)	
Epirubicin	€ 4,964.22
Oxaliplatin	€ 13,102.90
Capecitabine	€ 2,285.87
Total	€ 20,352.99
Epirubicin in combination with cisplatin and 5-fluorouracil (ECF)	
Epirubicin	€ 4,964.22
Cisplatin	€ 1,783.85
5-fluorouracil	€ 4,427.45
Total	€ 11,175.52
Additionally required SHI services	€ 328.58 - € 421.62
Epirubicin in combination with oxaliplatin and 5-fluorouracil	
Epirubicin	€ 4,964.22
Oxaliplatin	€ 13,102.90
5-fluorouracil	€ 4,427.45
Total	€ 22,531.11
S-1 (tegafur/ gimeracil/ oteracil) in combination with cisplatin	
S-1 (tegafur/ gimeracil/ oteracil)	€ 6,626.07
Cisplatin	€ 686.58
Total	€ 7,312.65
Additionally required SHI services	€ 113.30 - € 145.39

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient / year	Costs/ patient/ year
Medicinal product to be assessed					
Nivolumab in combination with 5-fluorouracil and folinic acid and oxaliplatin (FOLFOX-4)					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
5-fluorouracil *Bolus*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
5-fluorouracil *22 h infusion*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	2	52.2	€ 2,035.80
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Nivolumab in combination with 5-fluorouracil and folinic acid and oxaliplatin (modified FOLFOX-6)					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
5-fluorouracil *Bolus*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil *46 h infusion*	Surcharge for production of a parenteral preparation	€ 81	1	26.1	€ 2,114.10

	containing cytostatic agents				
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Nivolumab in combination with capecitabine and oxaliplatin (XELOX)					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17.4	€ 1,235.40
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Appropriate comparator therapy:					
Cisplatin in combination with 5-fluorouracil					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7047.00
Cisplatin in combination with 5-fluorouracil and folinic acid					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation	€ 81	5	87	€ 7,047.00

	containing cytostatic agents				
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	17.4	€ 678.60
Cisplatin + capecitabine (XP)					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Oxaliplatin in combination with 5-fluorouracil and folinic acid (FOLFOX-4)					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil *Bolus*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
5-fluorouracil *22 h infusion*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	2	52.2	€ 2,035.80
Oxaliplatin in combination with 5-fluorouracil and folinic acid (mod. FOLFOX-6)					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil *Bolus*	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil *46 h infusion*	Surcharge for production of a	€ 81	1	26.1	€ 2,114.10

	parenteral preparation containing cytostatic agents				
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
Oxaliplatin in combination with 5-fluorouracil and folinic acid (FLO)					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
Oxaliplatin in combination with capecitabine (XELOX)					
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Docetaxel in combination with cisplatin and 5-fluorouracil (DCF)					
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7,047.00

Docetaxel in combination with oxaliplatin and 5-fluorouracil and folinic acid (FLOT)					
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
Epirubicin in combination with cisplatin and capecitabine (ECX)					
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Epirubicin in combination with oxaliplatin and capecitabine (EOX)					
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Epirubicin in combination with cisplatin and 5-fluorouracil (ECF)					

Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	365	€ 29,565
Epirubicin in combination with oxaliplatin and 5-fluorouracil					
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Oxaliplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	365	€ 29,565
S-1 (tegafur/ gimeracil/ oteracil) in combination with cisplatin					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	6	€ 486