Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII - Resolutions on the benefit assessment of pharmaceuticals
with new active ingredients, in accordance with the German Social Code,
Book Five (SGB V), section 35a
Axitinib

from 21 March 2013

In its session on 21 March 2013, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 7 March 2013 (Federal Gazette, AT 10.04.2013 B5), as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient axitinib:

Axitinib

Therapeutic indication:

Inlyta® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

1. Additional benefit of the pharmaceutical over appropriate comparative treatment

a) Following previous treatment with sunitinib:

Appropriate comparator: everolimus

Extent and probability of additional benefit over everolimus:

An additional benefit has not been proved.

b) Following previous treatment with a cytokine:

Appropriate comparator: sorafenib

Extent and probability of additional benefit over sorafenib:

Indication of a minor additional benefit.

Study results according to endpoints[1]:

Mortality			
	Axitinib 25% quantile survival time [95% CI] N = 126	Sorafenib 25% quantile survival time [95% CI] N = 125	Axitinib vs. sorafenib HR [95% CI] p-value
Data cut-off 31 August 2010			
Overall survival[2]	15.9 months [11.6; n.e.]	12.2 months [10.7; n.e.]	0.744 [0.423; 1.307] 0.304
Data cut-off 1 November 2011			
Overall survival[2]	15.9 months [13.1; 22.5]	13.8 months [11.7; 18.0]	0.813 [0.555; 1.191] 0.288

Morbidity[3]			
FKSI-DRS score			
	Axitinib Time until worsening in FKSI-DRS[4]/ Patients with incident n (%)[5] N = 126	Sorafenib Time until worsening in FKSI-DRS[4]/ Patients with incident n (%)[5] N = 125	Axitinib vs. sorafenib HR [95% CI] p-value
Symptoms (FKSI-DRS), response	10.2 months/ 58 (46.0%)	7.6 months/ 55 (44.0%)	HR 0.933 [0.645; 1.351] 0.713

Health-related quality of life[3]			
FKSI-15 score			
	Axitinib Time until worsening in FKSI-15[6]/ Patients with incident n (%)[7] N = 126	Sorafenib Time until worsening in FKSI-15[6]/ Patients with incident n (%)[7] N = 125	Axitinib vs. sorafenib HR [95% CI] p-value
FKSI-15[6], response	12.9 months/ 56 (44.4%)	8.5 months/ 57 (45.6%)	HR 0.858 [0.593; 1.241] 0.416
EQ-5D	No analyses available for cytokine population		

Side effects[3]			
	Axitinib time until initial onset median [95% CI][8]/ Patients with incidents n (%) N = 126	Sorafenib time until initial onset median [95% CI][8]/ Patients with incidents n (%) N = 123	Axitinib vs. sorafenib HR [95% CI] p-value
AE	11 days [8; 15]/ 116 (92.1%)	7 days [5; 8]/ 120 (97.6%)	not interpretable[9]
Severe AE (CTCAE grade≥ 3)	166 days [96; 254]/ 74 (58.7%)	84 days [32; 155]/ 83 (67.5%)	0.750 [0.548; 1.026] 0.072

[1] From the dossier assessment conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) A12-14 for axitinib

[2] FAS assessment of intention-to-treat population

[3] Data as of: final assessment 31 August 2010

[4] Time until worsening, defined as decline of at least 3 points in comparison to condition at start of study

[5] Number of patients with worsening in FKSI-DRS by more than 2 points

[6] Time until worsening, defined as decline of at least 5 points in comparison to condition at start of study

[7] Number of patients with worsening in FKSI-DRS by more than 4 points

[8] Information on entry times refers to CTCAE grade; data for a comparison of entry times only for adverse events of CTCAE grades ≥ 3 are not available

[9] These could include e.g. a large number of temporary UEs. No information on this is available; it is therefore unclear what an effect would mean

Side effects[3]			
	Axitinib Time until initial onset median [95% CI][8]/ Patients with incidents n (%) N = 126	Sorafenib Time until initial onset median [95% CI][8]/ Patients with incidents n (%) N = 123	Axitinib vs. sorafenib HR [95% CI] p-value
SAE	n.e./ 27 (21.4%)	n.e./ 31 (25.2%)	0.790 [0.472; 1.324] 0.370
Terminations of treatment due to AE	n.e./ 7 (5.6%)	n.e./ 9 (7.3%)	0.715 [0.266; 1.922] 0.506
Frequent AE			
Alopecia all CTCAE grades	n.e./ 6 (4.8%)	n.e./ 44 (35.8%)	0.102 [0.043; 0.240] <0.001
CTCAE grade 2[10,11]	no incidents	no incidents	n/a
Reduced appetite all CTCAE grades	n.e./ 30 (23.8%)	n.e./ 23 (18.7%)	1.310 [0.760; 2.255] 0.330
CTCAE grades ≥ 3[10]	6 (4.8%)	3 (2.4%)	1.823 [0.458; 7.336] 0,8075[12]
Rash all CTCAE grades	n.e./ 17 (13.5%)	n.e./ 36 (29.3%)	0.396 [0.223; 0.706] 0.002
CTCAE grades ≥ 3[10]	no incidents	4 (3.3%)	n/a
Diarrhoea all CTCAE grades	227 days [141; 469]/ 62 (49.2%)	328 days [134; n.e.]/ 56 (45.5%)	0.954 [0.664; 1.369] 0.799
CTCAE grades ≥ 3[10]	12 (9.5%)	9 (7.3%)	1.196 [0.503; 2.841] 0,6572[12]
Dysphonia all CTCAE grades	n.e./ 38 (30.2%)	n.e./ 15 (12.2%)	2.643 [1.454; 4.807] 0.001
CTCAE grade 3[10,13]	no incidents	no incidents	n/a
Fatigue all CTCAE grades	n.e./ 46 (36.5%)	n.e./ 30 (24.4%)	1.624 [1.024; 2.573] 0.039
CTCAE grade 3[10,13]	15 (11.9%)	4 (3.3%)	3.613 [1.198; 10.9] 0,9927[12]
Chemotherapy-induced acral erythema all CTCAE grades	n.e./ 37 (29.4%)	45.0 days [21; 361]/ 71 (57.7%)	0.350 [0.235; 0.522] <0.001
CTCAE grade 3[10,13]	6 (4.8%)	23 (18.7%)	0.226 [0.092; 0.556] 0,0002[12]

[10] Data from the written hearing procedure

[11] There are no alopecia grades >2 in the CTCAE system

[12] p-value based on a 1-page unstratified log-rank test at level 0.025

[13] There are no dysphonia/fatigue/chemotherapy-induced acral erythema grades >2 in the CTCAE system

Side effects[3]			
	Axitinib Time until initial onset median [95% CI][8]/ Patients with incidents n (%) N = 126	Sorafenib Time until initial onset median [95% CI][8]/ Patients with incidents n (%) N = 123	Axitinib vs. sorafenib HR [95% CI] p-value
Hypertension			
all CTCAE grades	371 [59; n.e.] days 60 (47.6%)	n.e./ 52 (42.3%)	1.171 [0.808; 1.698] 0.405
CTCAE grades ≥ 3[10]	29 (23.0%)	19 (15.4%)	1.516 [0.850; 2.704] 0,9218[12]
Nausea			
all CTCAE grades	n.e./ 27 (21.4%)	n.e./ 14 (11.4%)	1.963 [1.029; 3.743] 0.041
CTCAE grades ≥ 3[10]	2 (1.6%)	1 (<1.0%)	n/a

Abbreviations used: CTCAE = common terminology criteria for adverse events; EQ-5D = EuroQol-5D; FAS = full analysis set; FKSI = functional assessment of cancer therapy – kidney symptom index; FKSI-DRS = functional assessment of cancer therapy kidney symptom index – disease-related symptoms; HR = hazard ratio; n/a = not available; CI = confidence interval; n.e. = no estimators; N = number of patients evaluated; n = number of patients with incidents; AE = adverse event; SAE = serious adverse event

2. Number of patients and criteria for defining patient groups eligible for treatment

a) Patients previously treated with sunitinib:

Percentage of target population: approx. 99%

Number of patients: approx. 914 patients

b) Patients previously treated with a cytokine:

Percentage of target population: approx 1%

Number of patients: approx. 6 patients

3. Requirements for quality-assured administration

The specifications outlined in the product information are to be followed. The European Medicines Agency (EMA), the European regulatory authority, provides the product information for Inlyta® (active ingredient: axitinib) at the following public link (last accessed: 23 January 2013): http://http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002406/WC500132188.pdf

In the European Public Assessment Report (EPAR), the EMA classifies the following side effects of axitinib as of particular interest: hypertension, thyroid disorders, arterial embolic and thrombotic events, elevated haemoglobin and haematocrit levels, bleeding, gastro-intestinal perforation, impaired healing of wounds, posterior reversible encephalopathy syndrome, proteinuria, adverse hepatic events, hepatic impairment, weakness, rash, chemotherapy-induced acral erythema, diarrhoea. Patients must be informed of risks mentioned and carefully monitored for relevant signs.

Treatment with axitinib must be administered by a physician experienced in the administration of oncological pharmaceuticals.

In the AXIS study, only patients with renal cell carcinoma with clear cell histology were examined. So far, sufficient data has not been collected on patients with non-clear cell renal cell carcinoma.

Furthermore, in accordance with the inclusion criteria, only patients with metastatic renal cell carcinoma were examined in the AXIS study. Patients with locally advanced renal cell carcinoma without (non-local) metastasis formation were not examined.

These patient groups are included in the therapeutic indication; however, as they were not or only insufficiently examined in the AXIS study, the data available for assessing the efficacy of ax for these patients is insufficient.

4. Costs of treatment

Duration of treatment[14]:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per year
Pharmaceutical evaluated				
Axitinib	ongoing, 2 x daily 5 –10 mg	ongoing	365	365
Appropriate comparator				
Everolimus	ongoing, 1 × daily 10 mg	ongoing	365	365
Sorafenib	ongoing, 2 × daily 400 mg	ongoing	365	365

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (tablets)[15]	Average annual consumption (tablets)
Pharmaceutical evaluated			
Axitinib	5	56	730 – 1,460
Appropriate comparator			
Everolimus	10	90	365
Sorafenib	200	112	1,460

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)[16]	Cost after legally mandated rebates
Pharmaceutical evaluated		
Axitinib	€5,596.68	€4,871.51 [€2.05[17]; €723.12[18]]
Appropriate comparator		
Everolimus	€14,051.45	€12,222.61 [€2.05[17]; €1,826.79[18]]
Sorafenib	€4,874.13	€4,243.28 [€2.05[17]; €628.80[18]]

("Lauer-Taxe", effective 1 March 2013)

Costs for additional, necessary statutory health insurance (SHI) benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Axitinib	€63,503.61 – 127,007.23
Appropriate comparator	
Everolimus	€49,569.47
Sorafenib	€55,314.19

[14] According to the product information, treatment should continue as long as a clinical benefit can be observed; calculation is standardized to 1 year

[15] Largest pack

[16] Largest pack

[17] Rebate in accordance with SGB V, section 130

[18] Rebate in accordance with SGB V, section 130a

II.

Validity

1. This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 21 March 2013.
2. This resolution remains valid until 21 March 2017.

The justification for this resolution will be published on the website of the Federal Joint Committee at www.g-ba.de.

Berlin, 21 March 2013

The Federal Joint Committee in
accordance with SGB V, section 91

The Chair
Hecken