Resolution

Gemeinsamer Bundesausschuss

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 According to Section 35a SGB V – Olaratumab

of 18 May 2017

At its session on 18 May 2017, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 15 June 2017 (Federal Gazette, BAnz AT 17 July 2017 B3), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient olaratumab as follows:

Olaratumab

Resolution of: 18 May 2017
Entry into force on: 18 May 2017
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved therapeutic indication (according to the marketing authorisation of 9 November 2016):

Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.

1. Extent of the additional benefit of the medicinal product

Olaratumab is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 10, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO). This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Extent of the additional benefit:

considerable

Study results according to endpoints:[1]

JGDG Phase 2 study: Olaratumab + doxorubicin vs doxorubicin

Endpoint	Olaratumab + doxorubicin		Doxorubicin		Olaratumab + doxorubicin vs doxorubicin
	N	Months (median) [95% CI]; Patients with event n (%)	N	Months (median) [95% CI]; Patients with event n (%)	Effect estimator [95% CI] p value
Mortality					
Overall survival	66	26.5[a)] [20.9; 31.7]; 39 (59.1)	67	14.7[a)] [9.2; 17.1]; 52 (77.6)	HR: 0.46 [0.30; 0.71] [b) c)]; p = 0.0003 [c) d)] AD: +11.8 months

[1] Data from the JGDG study - Phase 2 from the benefit assessment of the G-BA. The benefit assessment is based on the final data cut-off of 16 May 2015

Morbidity					
PFS[2] (independent review)	66	8.2 [5.5; 9.8]; 37 (56.1)	67	4.4 [3.1; 7.4]; 34 (50.7)	HR: 0.67 [0.40;1.12] b) c); p = 0.1208 c) d)
Quality of life					
No data were collected.					
Side effects					

	Olaratumab + doxorubicin f)		**Doxorubicin** f)		**Olaratumab + doxorubicin vs doxorubicin**
Endpoint	N g)	Patients with event n (%)	N g)	Patients with event n (%)	Effect estimator [95% CI] p value
Adverse events	64	63 (98.4)	65	64 (98.5)	no data available
Adverse event of NCI CTCAE grade ≥ 3		51 (79.7)		45 (69.2)	HR: 1.10 [0.73; 1.66]; p = 0.6348
Serious adverse event		27 (42.2)		25 (38.5)	HR: 0.70 [0.39; 1.24]; p = 0.2198
Therapy discontinuation because of adverse events h)		8 (12.5)		12 (18.5)	HR: 0.56 [0.23; 1.38]; p = 0.2025

Frequent adverse events (incidence ≥ 10% in one study arm) i)								
	Olaratumab + doxorubicin f)				**Doxorubicin** f)			
	N g)	Patients with event n (%)			N g)	Patients with event n (%)		
MedDRA System Organ Class Preferred Term		All grades	Grade 3	Grade 4		All grades	Grade 3	Grade 4
Blood and lymphatic system disorders	64	**45 (70.3)**	**14 (21.9)**	**21 (32.8)**	65	**41 (63.1)**	**14 (21.5)**	**12 (18.5)**
Neutropoenia		29 (45.3)	10 (15.6)	18 (28.1)		15 (23.1)	3 (4.6)	11 (16.9)
Anaemia		26 (40.6)	8 (12.5)	0		24 (36.9)	6 (9.2)	0
Leukopenia		16 (25.0)	9 (14.1)	5 (7.8)		5 (7.7)	2 (3.1)	2 (3.1)
Thrombocytopenia		14 (21.9)	4 (6.3)	2 (3.1)		12 (18.5)	3 (4.6)	2 (3.1)

[2] Data cut-off 15 August 2014

Frequent adverse events (incidence ≥ 10% in one study arm) [l]								
	Olaratumab + doxorubicin [f]				Doxorubicin [f]			
	N [g]	Patients with event n (%)			N [g]	Patients with event n (%)		
MedDRA System Organ Class Preferred Term		All grades	Grade 3	Grade 4		All grades	Grade 3	Grade 4
Febrile neutropoenia		8 (12.5)	7 (10.9)	1 (1.6)		9 (13.8)	9 (13.8)	0
Gastrointestinal disorders		**56 (87.5)**	**6 (9.4)**	**0**		**54 (83.1)**	**5 (7.7)**	**1 (1.5)**
Nausea	64	47 (73.4)	1 (1.6)	0	65	34 (52.3)	2 (3.1)	0
Vomiting		29 (45.3)	0	0		12 (18.5)	0	0
Diarrhoea		22 (34.4)	2 (3.1)	0		15 (23.1)	0	0
General disorders and administration site conditions		**55 (85.9)**	**8 (12.5)**	**0**		**56 (86.2)**	**4 (6.2)**	**0**
Mucosa inflammation		17 (26.6)	1 (1.6)	0		12 (18.5)	0	0
Investigations		**33 (51.6)**	**9 (14.1)**	**8 (12.5)**		**25 (38.5)**	**3 (4.6)**	**8 (12.3)**
Decreased neutrophil count		12 (18.8)	3 (4.7)	6 (9.4)		9 (13.8)	3 (4.6)	5 (7.7)
Low white blood cell count		12 (18.8)	6 (9.4)	4 (6.3)		7 (10.8)	3 (4.6)	4 (6.2)
Musculoskeletal and connective tissue disorders		**42 (65.6)**	**5 (7.8)**	**0**		**17 (26.2)**	**1 (1.5)**	**0**
Pain in the extremities		15 (23.4)	2 (3.1)	0		1 (1.5)	0	0
Back pain		12 (18.8)	2 (3.1)	0		6 (9.2)	0	0
Muscle spasms		10 (15.6)	0	0		1 (1.5)	0	0
Arthralgia		8 (12.5)	0	0		2 (3.1)	0	0
Musculoskeletal chest pain		8 (12.5)	1 (1.6)	0		2 (3.1)	0	0

Adverse events of special interest [g]								
	Olaratumab + doxorubicin [f]				Doxorubicin [f]			
	N [g]	Patients with event n (%)			N [g]	Patients with event n (%)		
Consolidated AE category		All grades	Grade 3	Grade 4		All grades	Grade 3	Grade 4
Any adverse events of special interest	64	24 (37.5)	1 (1.6)	2 (3.1)	65	21 (32.3)	1 (1.5)	0
Infusion-related reactions [i]		8 (12.5)	0	2 (3.1)		0	0	0
Cardiac arrhythmia [j]		10 (15.6)	0	0		10 (15.4)	1 (1.5)	0
Cardiac dysfunction [k]		15 (23.4)	1 (1.6)	0		11 (16.9)	0	0

a) Based on the Kaplan-Meier method
b) Cox Proportional Hazards Model
c) Stratification factors taken into account: Number of previous therapies (0 vs ≥ 1) and histological tumour sub-type (LMS vs others).
d) Log-rank test (two-sided)
e) Based on the significance level of 0.2 defined in the protocol for the primary PFS analysis and the α of 0.0001 used for the interim analysis, a significance level of 0.1999 was determined for the final PFS analysis.
f) Different treatment duration (median [weeks]) between intervention group (26.1 for olaratumab and 21.3 for doxorubicin) and control group (12.3 for doxorubicin).
g) Safety population: Number of patients with at least one dose of the study medication.
h) Termination of any study medication (intervention arm: olaratumab and/or doxorubicin; control arm: doxorubicin).
i) Includes 48 preferred terms.
j) PT: tachycardia, bradycardia, left bundle branch block, prolonged QT interval, increased heart rate, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, atrial fibrillation, supraventricular tachycardia, syncope
k) PT: peripheral oedema, reduced ejection fraction, cardiac insufficiency, hepatojugular reflux, jugular vein distension, left ventricular dysfunction
l) Selection based on the specific adverse events listed in the EPAR.

Abbreviations: HR: hazard ratio; CI: confidence interval; LMS: leiomyosarcoma; n: number; N: number of patients in the assessment; CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute; (S)AE: (serious) adverse event(s); PT: preferred term; MedDRA: Medical Dictionary for Regulatory Activities

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

approx. 1,200–1,400 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 Lartruvo® (active ingredient: olaratumab) at the following publicly accessible link (last access: 10 April 2017):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/004216/WC500216869.pdf

Treatment with olaratumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with soft tissue sarcomas.

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Designation of the therapy[3]	Annual treatment costs per patient
Olaratumab	€ 186,448.86
Doxorubicin	€ 3,200.56
Total	€ 189,649.42

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2017.

Costs for additionally required SHI services:

not applicable

Other services covered by SHI funds:

Surcharge for the preparation of a parenteral solution containing monoclonal antibodies and a parenteral product containing cytostatics.

Designation of the therapy[2]	Costs per unit	Number per cycle	Number per patient per year	Costs per patient per year
Olaratumab	€ 71	2	34	€ 2,414
Doxorubicin	€ 81	1	8	€ 648
Total				€ 3,062

[3] From the 2nd year of treatment onwards, the costs for olaratumab monotherapy apply.

II. Entry into force

1. **The resolution will enter into force from the day of its publication on the internet on the website of the G-BA on 18 May 2017.**
2. **The period of validity of the resolution is limited to 1 May 2020.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 18 May 2017

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken