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
Ataluren

From 21 May 2015

In its session on 21 May 2015, 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 16 April 2015 (Federal Gazette, AT 28 May 2015 B1), as follows:

I.

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

Ataluren

Therapeutic indication:

Ataluren (Translarna®) is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (see section 5.1 of the product information).

No efficacy was proved for non-ambulatory patients. The presence of a nonsense mutation in the dystrophin gene must be confirmed through genetic testing (see section 4.4 of the product information).

1. Extent of additional benefit of the pharmaceutical

   Ataluren is authorized as a pharmaceutical for the treatment of a rare disease in accordance with EC regulation number 141/2000 of the European Parliament and Council of 16 December 1999 on orphan drugs. In accordance with SGB V section 35a, paragraph 1, sentence 10, the additional medical benefit has been proved through market authorization.

   In accordance with the rules of procedure of the Federal Joint Committee, chapter 5, section 12, paragraph 1, number 1, sentence 2, the Federal Joint Committee determines the extent of the additional benefit for the number of patients and patient groups for whom a therapeutically significant additional benefit exists. This quantification of the additional benefit has been conducted in accordance with the criteria laid out in the rules of procedure, chapter 5, section 5, paragraph 7, numbers 1 to 4.

   Extent of additional benefit:

   Minor

   Study results according to endpoints[1]:

Mortality (48 weeks)
No deaths occurred during the study time

Morbidity					
Endpoint category Endpoint	Placebo (N = 57)		Ataluren[2] (N = 57)		Placebo vs. ataluren[2] Difference [95% CI] p-value
	BL	W. 48	BL	W. 48	
Walking distance 6MWT, MV (m)	359.6	317.4	350.0	342.7	26.44 [–4.21; 57.09] p = 0.0905 (nominal) p = 0.1592 (Dunnett)[3]

[1] Study 007, G-BA benefit assessment, ITT analysis.
[2] Ataluren dosage 10/10/20 mg.
[3] Dunnett-t procedure to include multiple comparisons.

Morbidity					
Endpoint category Endpoint	Placebo (N = 57)		Ataluren[2] (N = 57)		Placebo vs. ataluren[2] Difference [95% CI] p-value
	Events (percentage)		Events (percentage)		
6MWT at least 10% worsening	25 (43.9%)		15 (26.3%)		p = 0.0423
Time until at least 10% worsening					HR 0.52 [0.28; 0.966] p = 0.0386 (nominal) p = 0.078 (Dunnett)[3]
6MWT at least 10% improvement	6 (10.5%)		12 (21.1%)		p = 0.297
Time until at least 10% improvement					HR 1.675 [0.656; 4.277] p = 0.2805
	BL	W. 48	BL	W. 48	
Standing up from supine position, MV (s)	11.5	14.6	10.8	14.0	0 [–2.3; 2.3] p = 0.99[3]
10 m walking time, MV (s)	6.9	9.9	7.5	9.1	–1.3 [–3.7; 0.9] p = 0.40[3]
4 Climbing stairs time, MV (s)	6.0	10.8	6.9	9.3	–2.4 [–4.9; 0.1] p = 0.099[3]
4 Descending stairs time, MV (s)	5.5	9.6	6.1	8.5	–1.6 [–4.3; 1.0] p = 0.38[3]

Health-related quality of life (PedsQL)[4] Baseline, difference to W. 48					
	Placebo (N = 57)		Ataluren[2] (N = 57)		Placebo vs. ataluren[2]
Endpoint category Endpoint	BL	W. 48	BL	W. 48	LS-MV difference [95% CI]; p-value
PedsQL overall score	64.72	66.47	65.22	67.92	–0.11 [–5.95; 5.74] p = 0.9714
Physical subscale	61.87	59.53	59.27	62.61	3.56 [–4.31; 11.42] p = 0.37
Emotional subscale	70.13	73.8	73.7	72.82	–4.2 [–11.5; 3.05] p = 0.25
Social subscale	63.36	69.9	65.09	68.64	–2.38 [–9.52; 4.76] p = 0.51
School subscale	64.65	68.06	64.55	70.82	2.54 [–4.42; 9.5] p = 0.47
PedsQL fatigue scale	69.7	72.85	71.62	72.62	–2.41 [–8.85; 4.03] p = 0.46

Side effects: AE, SAE, withdrawal due to AE				
Endpoint category Endpoint	Placebo (N = 57)		Ataluren[2] (N = 57)	
	≥ 1 event	Percentage	≥ 1 event	Percentage
AE	56	98.2%	55	96.5%
SAE	3	5.3%	2	3.5%
Withdrawal due to AE	0	0	0	0
AE according to SOC (≥ 20% of patients)[5]				
Diseases of the gastrointestinal tract	37	64.9%	42	73.7%
General illnesses	21	36.8%	23	40.4%

[4] A higher score means better quality of life.

[5] Number of patients with ≥ 1 AE in the SOC according to MedDRA. Each patient is counted only once, even if several AEs or PTs occur for one SOC.

Side effects: AE, SAE, withdrawal due to AE				
Endpoint category Endpoint	Placebo (N = 57)		Ataluren[2] (N = 57)	
	≥ 1 event	Percen	≥ 1 event	Perce
Infections and parasitic diseases	43	75.4%	38	66.7%
Injuries, poisoning, and complications resulting from interventions	26	45.6%	28	49.1%
Diseases of the musculoskeletal system, connective tissue, and bones	19	33.3%	25	43.9%
Diseases of the nervous system	17	29.8%	25	43.9%
Diseases of the respiratory tract, chest cavity, and the mediastinum	18	31.6%	20	35.1%
Diseases of the skin and subcutaneous tissue	18	31.6%	19	33.3%

Abbreviations used: 6MWT = 6-minute walking test; BL = baseline; HR = hazard ratio; ITT = intention to treat; KI = confidence interval; PedsQL = Pediatric Quality of Life Inventory; PT = preferred term MedDRA; LS-MW = least square mean value; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; RR = relative risk; SOC = MedDRA system organ class; (S)AE = (serious) adverse events; W. = week

2. Number of patients and criteria for defining patients groups eligible for treatment, approx. 82 to 110

   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 contents of the product information for Translarna® (active ingredient: ataluren) at the following public link (last accessed: 9 April 2015): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002720/WC500171813.pdf

   Treatment with ataluren must be initiated and monitored by a specialist physician experienced in the treatment of patients with Duchenne/Becker muscular dystrophy.

   The pharmaceutical has been authorized under a so-called "conditional approval" scheme. That means that additional proof of benefit is expected for this pharmaceutical. The European Medicines Agency will assess new information on this pharmaceutical at least annually and update the product information as needed.

4. Costs of treatment

   Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per
Ataluren	ongoing, 3 × daily	ongoing	365	365

   Consumption:

Description of therapy	Strength (mg)	Quantity per pack (pouches)	Average annual consumption (pouches)[6]
Ataluren	40 mg/kg body weight	Granulate for producing an ingestible suspension; 125, 250, and 1,000 mg pouches	1,095 (125 mg pouches) + 1,460 (250 mg pouches)[7]

[6] Consumption for 33.12 kg body weight: average of the male population in each age group from 5 to 16 years (federal health report), weighted with the percentage of ambulatory patients in each age group.

[7] Dosage for 32 – 35 kg body weight according to product information: 1,375 mg daily, 3 x 125 mg + 4 x 250 mg.

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Ataluren (125 mg, 30 count)	€3,822.67	€3,605.86 [€1.77[8]; €215.04[9]]
Ataluren (250 mg, 30 count)	€7,588.02	€7,156.17 [€1.77[8]; €430.08[9]]

"Lauer-Taxe", effective: 1 April 2015

Costs for additional, necessary SHI benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Ataluren	€479,880.83

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 May 2015.
2. This resolution remains valid until 1 June 2016.

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

Berlin, 21 May 2015

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

The Chair
Prof. Hecken

[8] Rebate in accordance with SGB V, section 130.

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