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 – Ataluren (expiry of the deadline)

of 1 December 2016

At its session on 1 December 2016, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 20 October 2016 (Federal Gazette, BAnz AT 12.12.2016 B2), as follows:

I. Annex XII is amended as follows:

1. The information on ataluren in the version of the resolution of 21 May 2015 (Federal Gazette, BAnz AT 9 June 2015) is repealed.

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

Ataluren

Resolution of: 1 December 2016
Entry into force on: 1 December 2016
Federal Gazette, BAnz AT DD. MM YYYY Bx

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 has been demonstrated in non-ambulatory patients. The presence of a nonsense mutation in the dystrophin gene must be detected by genetic testing (see Section 4.4 of the product information).

1. Extent of the additional benefit of the medicinal product

Ataluren 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. In accordance with Section 35a, paragraph 1, sentence 10 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 the Rules of Procedure (VerfO) of the G-BA. 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:

Minor additional benefit

Study results by endpoint (PTC124-GD-020-DMD (020) and PTC124-GD-007-DMD (007) studies):

<table>
<tr><th colspan="6">Mortality (48 weeks)</th></tr>
<tr><td colspan="6">No deaths occurred in study 007 or study 020 during the study period</td></tr>
<tr><th colspan="6">Morbidity</th></tr>
<tr><th colspan="6">020 study</th></tr>
<tr><th>Endpoint category
Endpoint</th><th colspan="2">Placebo (N = 114)</th><th colspan="2">Ataluren (N = 114)</th><th>LS mean difference [95% CI]
p value</th></tr>
<tr><td>Walking distance 6MWT[a] (metres)</td><td>BL</td><td>W 48</td><td>BL</td><td>W 48</td><td></td></tr>
<tr><td rowspan="2">Absolute change[b]</td><td>363.5</td><td>306.5</td><td>365.2</td><td>326.3</td><td rowspan="2">n.s.</td></tr>
<tr><td colspan="2">AD: -57.6</td><td colspan="2">AD: -42.2</td></tr>
<tr><td>Change in group comparison</td><td colspan="4"></td><td>12.98[c] [-7.44; 33.39]
p = 0.213</td></tr>
<tr><td>Subgroup analysis</td><td colspan="4"></td><td></td></tr>
<tr><td rowspan="2">BL < 300</td><td>233.5</td><td>96.8</td><td>256.9</td><td>129.2</td><td rowspan="2">-7.71 [-54.93; 39.51]
p = 0.749</td></tr>
<tr><td colspan="2">N = 21</td><td colspan="2">N = 24</td></tr>
<tr><td rowspan="2">BL ≥ 300 to < 400</td><td>354.5</td><td>278.0</td><td>356.7</td><td>328.9</td><td rowspan="2">AD[b] = 48.7
42.89 [11.75; 74.03]
p = 0.007</td></tr>
<tr><td colspan="2">N = 52
AD[b] = -76.5</td><td colspan="2">N = 47
AD[b] = -27.8</td></tr>
<tr><td rowspan="2">BL ≥ 400</td><td>441.6</td><td>441.8</td><td>435.0</td><td>429.9</td><td rowspan="2">-9.51 [-43.19; 24.18]
p = 0.58</td></tr>
<tr><td colspan="2">N = 41</td><td colspan="2">N = 43</td></tr>
<tr><td rowspan="2">BL < 350</td><td>276.7</td><td>153.0</td><td>285.6</td><td>189.3</td><td rowspan="2">21.89 [-12.32; 56.11]
p = 0.21</td></tr>
<tr><td colspan="2">N = 41</td><td colspan="2">N = 41</td></tr>
<tr><td rowspan="2">BL ≥ 350</td><td>412.3</td><td>392.0</td><td>409.9</td><td>399.7</td><td rowspan="2">7.98 [-1.53; 33.48] p = 0.54</td></tr>
<tr><td colspan="2">N = 73</td><td colspan="2">N = 73</td></tr>
<tr><td>Time to persistent deterioration by at least 10%</td><td colspan="4">N
Events (percentage %)</td><td>HR [95% CI] p value</td></tr>
<tr><td>Deterioration by at least 10%</td><td colspan="3">114
52 (45.6)</td><td colspan="2">114
49 (43.0)</td><td>0.75 [0.51; 1.12]
p = 0.1603</td></tr>
<tr><td>Subgroup analysis</td><td colspan="4">N
Median time (days) [95% CI]</td><td>HR [95% CI] p value</td></tr>
<tr><td>< 300 metres</td><td colspan="3">21
56 [1.0; 111.0]</td><td colspan="2">24
164 [1.0; 225.0]</td><td>0.48 [0.24; 0.93]
p = 0.031</td></tr>
<tr><td>≥ 300 metres to < 400 metres</td><td colspan="3">52
280 (169.9;-)</td><td colspan="2">47
(280;-)</td><td>0.79 [0.44; 1.41]
p = 0.42</td></tr>
<tr><td>≥ 400 metres</td><td colspan="3">41
n.s.</td><td colspan="2">43
n.s.</td><td>1.52 [0.59; 3.91]
p = 0.39</td></tr>
</table>

Endpoint category Endpoint	Placebo		Ataluren		LS mean difference [95% CI] p value
Change TFT at week 48	**BL**	**W 48**	**BL**	**W 48**	
10 m run/ walk Time, MV (s)	6.8	10.3	6.6	8.8	-1.07 [-2.4; 0.27] p = 0.12
Climb up 4 steps Time, MV (s)	6.4	10.6	5.9	8.8	-1.4 [-2.9; 0.05] p = 0.06
Climb down 4 steps Time, MV (s)	4.8	9.3	5.0	7.4	-1.97 [-3.52; -0.43] p = 0.01
	AD[b] = 4.5		AD[b] = 2.4		
Total score NSAA	21.9	18.4	22.2	20.1	0.80 [-0.23; 1.82] p = 0.13
Linearised score NSAA	60.2	52.2	60.9	55.7	1.51 [-1.16; 4.17] p = 0.27
007 study					
Endpoint category Endpoint	**Placebo (N = 57)**		**Ataluren (N = 57)** Dosage 10/10/20 mg/kg BW		**LS mean difference [95% CI] p value**
Walking distance 6MWT[a]	**BL**	**W 48**	**BL**	**W 48**	
MV (m)	359.6	317.4	350.0	342.7	26.44 [-4.21; 57.09] p = 0.09
Change in group comparison	**Events (percentage %)**				**HR [95% CI] p value**
Deterioration by at least 10%	25 (43.9%)		15 (26.3%)		p = 0.0423
Time to at least 10% deterioration					HR 0.52 [0.28; 0.966] p = 0.0386
6MWT improve-ment by at least 10%	6 (10.5%)		12 (21.1%)		p = 0.297
Time to at least 10% improvement					HR 1.675 [0.656; 4.277] p = 0.28
Change TFT at week 48	**BL**	**W 48**	**BL**	**W 48**	**Difference [95% CI] p value**
Standing up from supine position Time, MV (s)	11.5	14.6	10.8	14.0	0 [-2.3; 2.3] p = 0.99
10 m run/ walk Time, MV (s)	6.9	9.9	7.5	9.1	-1.3 [-3.7; 0.9] p = 0.40

Endpoint category Endpoint	Placebo		Ataluren		LS mean difference [95% CI] p value
Climb up 4 steps Time, MV (s)	6.0	10.8	6.9	9.3	-2.4 [-4.9; 0.1] p = 0.099
Climb down 4 steps Time, MV (s)	5.5	9.6	6.1	8.5	-1.6 [-4.3; 1.0] p = 0.38
Health-related quality of life					
020 study					
Health-related quality of life (PODCI)[d]					
Endpoint category Endpoint	**BL**	**W 48**	**BL**	**W 48**	**LS MV difference [95% CI] p value**
Transfer/ basic mobility subscale	81.4	72.4	83.9	77.2	1.64 [-2.11; 5.39] p = 0.39
Sport/ physical functioning sub-scale	56.0	48.3	56.2	51.1	2.15 [-1.75; 6.05] p = 0.28
007 study					
Health-related quality of life PedsQL[d]					
Endpoint category Endpoint	**BL**	**W 48**	**BL**	**W 48**	**LS MV difference [95% CI] p value**
Physical subscale	61.87	59.53	59.27	62.61	3.56 [-4.31; 11.42] p = 0.37
Emotional sub-scale	70.13	73.8	73.7	72.82	-0.42 [-11.5; 3.05] p = 0.25
Social subscale	63.36	69.9	65.09	68.64	-2.38 [-9.52; 4.76] p = 0.051
School subscale	64.65	68.06	64.55	70.82	2.54 [-4.42; 9.5] p = 0.47
Fatigue scale	69.7	72.85	71.62	72.62	-2.41 [-8.85; 4.03] p = 0.46

Side effects		
020 study		
Endpoint	**Placebo (N = 115)**	**Ataluren (N = 115)**
AEs, severity grade, discontinuation due to AEs, SAEs	**Patients with at least one event: N (percentage %)**	
AE	101 (87.8)	103 (89.6)
AEs according to severity grade Grade 1 (mild) Grade 2 (moderate) Grade 3 (severe) Grade 4 (life-threatening)	 54 (47.0) 37 (32.2) 9 (7.8) 0	 61 (53.0) 35 (30.4) 7 (6.1) 0
Discontinuation due to AEs	1 (0.9)	1 (0.9)
SAE	4 (3.5)	4 (3.5)
AEs according to SOC/ preferred term MeDRA[e]	**Patients with at least one event: N (percentage %)**	
Gastrointestinal tract	48 (41.7)	52 (45.2)
General diseases	32 (27.8)	29 (25.2)
Infections	50 (43.5)	63 (54.8)
Injury, poisoning and procedural complications	34 (29.6)	35 (30.4)
Musculoskeletal and connective tissue	32 (27.8)	32 (27.8)
Nervous system	23 (20.0)	28 (24.3)
Respiratory tract, thorax, mediastinum	30 (26.1)	34 (29.6)
AEs according to SOC/ preferred term MeDRA with severity grade ≥ 3	**Patients with at least one event: N (percentage %)**	
Blood and lymphatic system	0	1 (0.9)
Gastrointestinal tract	1 (0.9)	2 (1.7)
General diseases	7 (6.1)	4 (3.5)
Infections	0	1 (0.9)
Injury, poisoning and procedural complications	0	2 (1.7)
Musculoskeletal and connective tissue	3 (2.6)	1 (0.9)
Treatment-associated hepatic and renal AEs according to SOC/ preferred term MeDRA	**Patients with at least one event: N (percentage %)**	
≥ 1 treatment-associated hepatic or renal AE	9 (7.8)	15 (13.0)
General diseases	0	3 (2.6)
Hepatobiliary disorders	1 (0.9)	0
Renal and urinary tract disorders	8 (7.0)	12 (10.4)

007 study		
Endpoint	**Placebo (N = 57)**	**Ataluren (N = 57)** Dosage 10/10/20 mg/kg BW
AEs, severity grade, discontinuation due to AEs, SAEs	**Patients with at least one event: N (percentage %)**	
AE	56 (98.2)	55 (96.5)
AEs according to severity grade Grade 1 (mild) Grade 2 (moderate) Grade 3 (severe) Grade 4 (life-threatening)	 21 (36.8) 26 (45.6) 9 (15.8) 0	 16 (28.1) 31 (54.4) 8 (14) 0
Discontinuation due to AEs	0	0
SAE	3 (5.3)	2 (3.5)
AEs according to SOC/ preferred term MeDRA[e]	**Patients with at least one event (with percentage ≥ 20%): N (percentage %)**	
Gastrointestinal tract	37 (64.9)	42 (73.7)
General diseases	21 (36.8)	23 (40.4)
Infections	43 (75.4)	38 (66.7)
Injury, poisoning and procedural complications	26 (45.6)	28 (49.1)
Musculoskeletal and connective tissue	19 (33.3)	25 (43.9)
Nervous system	17 (29.8)	25 (43.9)
Respiratory tract, thorax, mediastinum	18 (31.6)	20 (35.1)
Skin, subcutaneous tissue	18 (31.6)	19 (33.3)
AEs according to SOC/ preferred term MeDRA with severity grade ≥ 3	**Patients with at least one event: N (percentage %)**	
Blood and lymphatic system	0	0
Gastrointestinal tract	1 (1.8)	2 (3.5)
General diseases	6 (10.5)	4 (7)
Infections	0	0
Injury, poisoning and procedural complications	1 (1.8)	2 (3.5)
Musculoskeletal and connective tissue	0	2 (3.5)

a) 23 patients lost their ability to walk during the course of the study, the 6MWT values of these patients were registered as 0 from the time of loss of ability to walk.
b) Indication only in case of significant group differences
c) ANCOVA model with change from baseline as dependent variable, independent variables. Stratification factors (age < 9/ ≥ 9 years; baseline 6MWT < 350/ ≥ 350 m; duration of corticosteroid therapy (≥ 6 to < 12/ ≥ 12 months), therapy, baseline 6MWT as covariates
d) The higher the score, the better the quality of life
e) Frequency ≥ 5% of patients

6MWT = 6-minute walk test; BL = Baseline; HR = Hazard ratio; ITT = intention to treat; CI = confidence interval; LS-MV = least square mean value; MedDRA = Medical Dictionary for Regulatory Activities; n.s. = not to be specified; N = Number of patients; PedsQL = Paediatric Quality of Life Inventory; PODCI = Paediatric Outcomes Data Collection Instrument; PT = preferred term; SOC = system organ class of MedDRA; (S)AE = (serious) adverse events; TFT = Timed Function Test; W = week

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

approx. 30 to 40 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 Translarna™ (active ingredient: ataluren) at the following publicly accessible link (last access: 13 October 2016; http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002720/WC500171813.pdf

Treatment with ataluren should only be initiated and monitored by specialists who are experienced in the treatment of patients with Duchenne/Becker muscular dystrophy.

This medicinal product received a conditional marketing authorisation. 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	Annual treatment costs per patient
Ataluren[1]	-

II. Entry into force

The resolution will enter into force on the day of its publication on the internet on the website of the Federal Joint Committee on 1 December 2016.

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

Berlin, 1 December 2016

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

Prof. Hecken

[1] The pharmaceutical company discontinued the proprietary medicinal product Translarna (active ingredient ataluren) from the market on 1 April 2016.
A reimbursement amount for Ataluren was set by the Joint Arbitration Board under Section 130b paragraph 5 SGB V pursuant to Section 130b paragraph 4 SGB V. Pursuant to Section 23 paragraph 1 of the Rules of Procedure of the Joint Arbitration Board under Section 130b paragraph 5 SGB V, the decisions pursuant to Section 130b paragraphs 4, 7 and 9 may be inspected at the office of the Arbitration Board.