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
Aclidinium bromide / formoterol

From 16 July 2015

In its session on 16 July 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 21 May 2015 (Federal Gazette, AT 5 August 2015 B1) as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient aclidinium bromide/formoterol:

Aclidinium bromide/formoterol

Therapeutic indication:
Aclidinium bromide/formoterol (Duaklir® Genuair®/Brimica® Genuair®) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

1. Additional benefit of the pharmaceutical over appropriate comparator

Subpopulation a)

Patients with moderate severity COPD 50% ≤ FEV_1 < 80% target (stage II)

Appropriate comparator:

- long-acting beta2-adrenergic agonists (formoterol or salmeterol) or long-acting anticholinergics (tiotropium bromide) or the combination of both classes of active ingredients

Extent and probability of additional benefit over treatment with the long-acting beta2-adrenergic agonist formoterol:

Indication of a minor additional benefit

Subpopulation b)

COPD patients with < 2 exacerbations per year, 30% ≤ FEV_1 < 50% target (stage III)

Appropriate comparator:

- long-acting beta2-adrenergic agonists (formoterol or salmeterol) or long-acting anticholinergics (tiotropium bromide) or the combination of both classes of active ingredients

Extent and probability of additional benefit over treatment with the long-acting beta2-adrenergic agonist formoterol:

Indication of a considerable additional benefit

Subpopulation c)

COPD patients with < 2 exacerbations per year, FEV_1 < 30% target, or respiratory insufficiency (stage IV)

Appropriate comparator:

– long-acting beta2-adrenergic agonists (formoterol or salmeterol) or long-acting anticholinergics (tiotropium bromide) or the combination of both classes of active ingredients

Extent and probability of additional benefit over treatment with the long-acting beta2-adrenergic agonist formoterol:

An additional benefit has not been proved

Subpopulation d)

Patients with greater than moderate severity COPD 30% ≤ FEV_1 < 50% target or FEV_1 < 30% or respiratory insufficiency (stages III and IV) with ≥ 2 exacerbations per year

Appropriate comparator:

– long-acting beta2-adrenergic agonists (formoterol or salmeterol) or long-acting anticholinergics (tiotropium bromide) or the combination of both classes of active ingredients, with additional inhalative corticosteroids (ICS)

Extent and probability of additional benefit over treatment with the long-acting beta2-adrenergic agonist formoterol with additional ICS:

An additional benefit has not been proved.

For patient populations a) and b): study results according to endpoints[1]:

Endpoint category	Aclidinium bromide/formoterol		Formoterol		Aclidinium bromide/formoterol vs. formoterol	
Endpoint Study	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p-value	RR [95% CI[2]] p-value
Mortality						
Overall mortality						
ACLIFORM	182	0 (0)	195	1 (0.5)		n.i.
AUGMENT	211	1 (0.5)	198	0 (0)		n.i.
LAC-MD-32	220	2 (0.9)	115	0 (0)		n.i.
Overall						1.41 [0.23; 8.65] 0,708[3]
Morbidity						
Moderate exacerbations (HCRU)						
ACLIFORM	182	9 (4.9)	195	22 (11.3)		0.44 [0.21; 0.93] 0,031[4]
AUGMENT	211	23 (10.9)	198	18 (9.1)		1.20 [0.67; 2.15] 0,543[4]
LAC-MD-32	220	44 (20.0)	115	25 (21.7)		0.92 [0.59; 1.42] 0,708[4]
Overall	Heterogeneity[3]: Q = 4.46; df = 2; p = 0.108, I^2 = 55.1					
Severe exacerbations (HCRU)						
ACLIFORM	182	2 (1.1)	195	1 (0.5)		2.14 [0.20; 23.43] 0,532[4]
AUGMENT	211	1 (0.5)	198	4 (2.0)		0.23 [0.03; 2.08] 0,193[4]

[1] The results of the comparison of aclidinium bromide/formoterol to formoterol in patients with COPD stage II and patients with COPD stage III with fewer than two exacerbations per year are shown together. Wherever necessary, the data from the dossier submitted by the pharmaceutical company have been supplemented by IQWiG calculations. No data were submitted for patients with COPD stage IV with fewer than two exacerbations per year. No results are shown for COPD stage III patients with more than two exacerbations per year because no statistically significant results were observed.

[2] The RR are calculated for determining the additional benefit based on the OR and the estimated basis risk in the IQWiG comparison group. All drop-outs were counted as non-responders and are shown only in cases of significant OR.

[3] IQWiG calculation from meta-analysis

[4] Effect from logistic regression model.

Endpoint category Endpoint Study	Aclidinium bromide/formoterol N	 Patients with event n (%)	Formoterol N	 Patients with event n (%)	Aclidinium bromide/formoterol vs. formoterol OR [95% CI]; p-value	 RR [95% CI[2]] p-value
LAC-MD-32	220	7 (3.2)	115	8 (7.0)[5]		0.46 [0.17; 1.23] 0,121[4.5]
Overall						0.50 [0.22; 1.17] 0,109[4]
Severe exacerbations (HCRU) for subgroup according to severity level stage II and III						
ACLIFORM						
Stage II	124	2 (1.6)	132	1 (0.8)		2.13 [0.22; 1.17] 0.532
Stage III	58	0 (0)	63	0 (0)		n.c.
AUGMENT						
Stage II	137	1 (0.7)	130	2 (1.5)		0.47 [0.04; 5.17] 0.541
Stage III	74	0 (0)	68	2 (2.9)		0.18 [0.01; 0.151[7]
LAC-MD-32						
Stage II	134	3 (2.2)	68	0 (0.0)		3.58 [0.19; 0.233
Stage III	86	4 (4.7)	47	8 (17.0)[5]		0.27 [0.09; 0.027[5]
Overall						Interaction 0.072[3]
Stage II						1.38 [0.32; 5.95][3]; 0.670[3]
Stage III						0.26 [0.09; 0.76][3]; 0.014[3]
COPD symptoms (TDI responders)[8]						
ACLIFORM	182	115[9] (63.2)[10]	195	106[9] (54.4)[10]	1.41 [0.80; 2.47][11];	
AUGMENT	211	100[9] (47.4)[10]	198	83[9] (41.9)[10]	1.72 [0.97; 3.02][11];	
LAC-MD-32	Endpoint not					
Overall					1.54 [1.04; 2.29][12];	1.22 [1.04; 1.44] 0.017[13]
Severe exacerbations (TDI responders)[8] for subgroup according to severity level stage II and III						
ACLIFORM						
Stage II	124	74[9] (59.7)[10]	132	72[9] (54.5)[10]	1.24 [0.64; 0.522	
Stage III	58	41[9] (70.7)[10]	63	34[9] (54.0)[10]	1.91 [0.67; 0.225	
AUGMENT						
Stage II	137	63[9] (46.0)[10]	130	58[9] (44.6)[10]	1.32 [0.65; 0.44	
Stage III	74	37[9] (50.0)[10]	68	25[9] (36.8)[10]	2.87 [1.08; 0.035	
LAC-MD-32	Endpoint not recorded					

[5] Discrepancy between information in module 4 A and module 5 of the dossier. The figures shown are from the additional analyses of the pharmaceutical company in module 5.

[6] IQWiG calculation with continuity correction.

[7] p-value from CSZ test, IQWiG calculation

[8] Patients with TDI overall score≥ 1.

[9] Patients with response by end of study. These figures are for information only and were not used to calculate the OR or relative risk.

[10] Percentages self-calculated based on ITT population.

[11] OR determined through a priori defined logistic regression model and taking missing values into account using the direct likelihood method based on the ITT population.

[12] IQWiG calculation from the IPD meta-analysis

[13] IQWiG calculation of RR based on the effect measure OR given and the basis risk of the control arm (drop-out shown as non-responders).

Endpoint category Endpoint Study	Aclidinium bromide/formoterol N	 Patients with event n (%)	Formoterol N	 Patients with event n (%)	Aclidinium bromide/formoterol vs. formoterol OR [95% CI]; p-value	 RR [95% CI[2]] p-value
Overall					Interaction 0.169[12]	
Stage II					1.27 [0.78; 2.06] 0.332[12]	1.12 [0.91; 1.39] 0.292[13]
Stage III					2.31 [1.14; 4.68] 0.020[12]	1.46 [1.106; 0.008[13]
COPD symptoms (E-RS overall score responders[14])						
ACLIFORM	182	67[9] (36.8)[10]	194	57[9] (29.4)[10]	1.60 [0.93; 0.088	
AUGMENT	211	80[9] (37.9)[10]	198	51[9] (25.8)[10]	1.89 [1.14; 0.014	
LAC-MD-32						
Overall					1.75 [1.21; 2.53] 0.003	1.45 [1.16; 1.81] 0.001
COPD symptoms (E-RS overall score responders)[14] for subgroup according to severity level stage II and III						
ACLIFORM						
Stage II	124	45[9] (36.3)[10]	131	40[9] (30.6)[10]	1.43 [0.74; 0.290	
Stage III	58	22[9] (37.9)[10]	63	17[9] (27.0)[10]	2.02 [0.77; 0.151	
AUGMENT						
Stage II	137	63[9] (46.0)[10]	130	32[9] (24.6)[10]	1.46 [0.77; 0.249	
Stage III	74	63[9] (48.6)[10]	68	19[9] (27.9)[10]	2.97 [1.29; 0.010	
LAC-MD-32	Endpoint not recorded					
Overall					Interaction 0.185[12]	
stage II					1.46 [0.92; 2.30] 0.106[12]	1.29 [0.96; 1.73] 0.095[13]
Stage III					2.45 [1.32; 4.56] 0.005[12]	1.80 [1.31; 2.47] < 0.001[13]
Health-related quality of life SGRQ responders[15]						
ACLIFORM	182	93[9] (51.1)[10]	195	97[9] (49.7)[10]	1.05 [0.59; 1.85][11];	
AUGMENT	211	100[9] (47.4)[10]	198	75[9] (37.9)[10]	1.70 [0.94; 3.08][11];	
LAC-MD-32	Endpoint not recorded					
Overall Side effects AE					1.34 [0.89; 2.02][12];	
ACLIFORM	182	88 (48.4)	195	106 (54.4)		
AUGMENT	211	132 (62.6)	198	106 (53.5)		
LAC-MD-32	220	149 (67.7)	115	76 (66.1)		

[2] The RR are calculated for determining the additional benefit based on the OR and the estimated basis risk in the IQWiG comparison group. All drop-outs were counted as non-responders and are shown only in cases of significant OR.

[14] E-RS overall score responders: Reduction of≥ 3.35 points

[15] Patients with reduction in SGRQ overall score of≥ 4.

Endpoint category Endpoint Study	Aclidinium bromide/formoterol N	 Patients with event n (%)	Formoterol N	 Patients with event n (%)	Aclidinium bromide/formoterol vs. formoterol OR [95% CI]; p-value	 RR [95% CI[2]] p-value
SAE						
ACLIFORM	182	9 (4.9)	195	10 (5.1)		0.96 [0.40; 2.32] 0.935
AUGMENT	211	12 (5.7)	198	4 (2.0)		2.82 [0.92; 8.58] 0.069
LAC-MD-32	220	23 (10.5)	115	13 (11.3)		0.92 [0.49; 1.76] 0.811
Overall						1.21 [0.65; 2.22]; 0.548[3]
Withdrawal due to AE						
ACLIFORM	182	4 (2.2)	195	5 (2.6)		0.86 [0.23; 3.14] 0.816
AUGMENT	211	13 (6.2)	198	6 (3.0)		2.03 [0.79; 5.25] 0.142
LAC-MD-32	220	14 (6.4)	115	6 (5.2)		1.22 [0.48; 3.09] 0.675
Overall						1.38 [0.77; 2.50]; 0.282[3]

COPD: chronic obstructive pulmonary disease
E-RS: exacerbations of chronic pulmonary disease tool respiratory symptoms
IPD: individual patient data
ITT: intention to treat
CI: confidence interval
N: number of patients evaluated; n: Number of patients with event
n.c.: not calculable
OR: odds ratio
RR: relative risk
SGRQ: St George's respiratory questionnaire
TDI: transition dyspnea index
HCRU: healthcare resource utilization
n.i.: no information

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

Subpopulation a) approx. 2,016,500 to 2,381,500

Subpopulation b) approx. 128,100 to 151,200

Subpopulation c) approx. 12,000 to 15,200

Subpopulation d) approx. 181,700 to 214,600

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 Duaklir® Genuair®/Brimica® Genuair® (active ingredient: aclidinium bromide/formoterol) at the following public link (last accessed: 10 June 2015):

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003745/WC500178413.pdf

4. Costs of treatment

Duration of treatment:

Designation 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				
Aclidinium bromide /formoterol[16]	ongoing, 2 × daily	ongoing	365	365
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional[17]				

[16] According to the product information, two individual doses should be taken daily.

[17] Duration of treatment, consumption, and costs indicated for inhalative corticosteroids are examples for the active ingredients beclometasone and fluticasone

Designation of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per year
Beclometasone	ongoing, 2 x daily	ongoing	365	365
Fluticasone	ongoing, 2 x daily	ongoing	365	365
Appropriate comparator				
Tiotropium bromide	ongoing, 1 × daily	ongoing	365	365
And/or long-acting beta2-adrenergic agonists				
Formoterol	ongoing, 2 × daily	ongoing	365	365
salmeterol	ongoing, 2 × daily			
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional				
Beclometasone	ongoing, 2 x daily	ongoing	365	365
Fluticasone	ongoing, 2 x daily	ongoing	365	365

Consumption:

Designation of therapy	Strength/ individual dose	Quantity per pack (individual doses[18])[19]	Average annual consumption (individual doses)
Pharmaceutical evaluated			
Aclidinium bromide/formoterol	340 µg/12 µg	180	730
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional			
Beclometasone[20]	200 µg	400	730
Fluticasone[21]	500 µg	120	730
Appropriate comparator			
Tiotropium bromide	18 µg	90	335
		30[22]	30
And/or long-acting beta2-adrenergic agonists			
Formoterol	12 µg	180	730
Salmeterol[23]	25 µg	240	1,460
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional			
Beclometasone[20]	200 µg	400	730
Fluticasone	500 µg	120	730

[18] Capsules for inhalation (powder inhalator) or puffs (pressurized gas inhalator).

[19] Largest pack.

[20] According to the beclometasone product information, the recommended dosage ranges from 0.4 mg per day to 1 mg per day, divided into two doses. The maximum dosage of 2 mg per day is not considered. Two puffs of 0.2 mg each per day are shown here as an example for the calculation. (Beclometasone product information; effective: April 2014).

[21] According to the fluticasone product information, the recommended dosage is 500 µg twice a day (Flutide Diskus product information; effective: October 2014).

[22] One time per year the combination pack of 30 individual doses and an inhalator for tiotropium bromide.

[23] According to the product information, the dosage of salmeterol is 50 µg twice a day. The calculation here is based on two puffs each (25 µg). The maximum dosage of 200 µg per day is not considered (salmeterol HEXAL® product information; effective: February 2012).

Costs:

Designation of therapy	Cost (pharmacy retail price)[24]	Cost after legally mandated rebates
Pharmaceutical evaluated		
Aclidinium bromide/formoterol	€214.66	€201.61 [€1.77[25]; €11.28[26]]
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional		
Beclometasone[27] Fluticasone[27]	€65.52 €45.22	€59.44 [€1.77[25]; €4.31[26]] €40.74 [€1.77[25]; €2.71[26]]
Appropriate comparator		
Tiotropium bromide	€176.30 €69.15[22]	€160.37 [€1.77[25]; €14.16[26]] €62.40 [€1.77[25]; €4.99[26]]
And/or long-acting beta2-adrenergic agonists		
Formoterol Salmeterol	€86.18[27] €79.22[27]	€78.46[€1.77[25]; €5.95[26]] €72.05[€1.77[25]; €5.40[26]]
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional		
Beclometasone Fluticasone	€65.52[27] €45.22[27]	€59.41 [€1.77[25]; €4.31[26]] €40.71 [€1.77[25]; €2.71[26]]

Costs for additional, necessary SHI benefits: none

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Aclidinium bromide/formoterol €817.64	
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional	
Beclometasone Fluticasone	€108.47 €247.84
Appropriate comparator	
Tiotropium bromide	€659.32
And/or long-acting beta2-adrenergic agonists	
Formoterol Salmeterol	€318.21 €438.32
For COPD patients stage III and higher with ≥ 2 exacerbations per year, inhalative corticosteroids additional	
Beclometasone Fluticasone	€108.47 €247.84

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 16 July 2015.

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

Berlin, 16 July 2015

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

The Chair

Prof. Hecken

[24] "Lauer-Taxe", effective: 15 June 2015.

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

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

[27] Reference price level II.