Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL) Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Beclometasone/formoterol/glycopyrronium (first dossier requirement: Asthma)

of 5 August 2021

At its session on 5 August 2021, the Federal Joint Committee (G-BA) resolved to amend the 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 DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient beclometasone/formoterol/glycopyrronium as follows:

Beclometasone/formoterol/glycopyrronium

Resolution of: 5 August 2021
Entry into force on: 5 August 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to marketing authorisation):

Potency 87/5/9 µg:

Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

Potency 172/5/9 µg:

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year

Therapeutic indication of the resolution (resolution of 5 August 2021):

Potency 87/5/9 µg:

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

Potency 172/5/9 µg:

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) adults with asthma who are not adequately controlled with medium-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

Appropriate comparator therapy:

a patient-individual therapy escalation taking into account the previous therapy, the severity of the disease and the symptomatology under the selection of:

- medium-dose ICS and LABA and LAMA or
- high-dose ICS and LABA

Extent and probability of the additional benefit of beclometasone/formoterol/glycopyrronium compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) adults with asthma who are not adequately controlled with high-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

Appropriate comparator therapy:

- high-dose ICS and LABA and LAMA

Extent and probability of the additional benefit of beclometasone/formoterol/glycopyrronium compared to beclometasone/formoterol + tiotropium:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) adults with asthma who are not adequately controlled with medium-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

There are no data.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-18) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available
Morbidity	∅	No data available
Health-related quality of life	∅	No data available
Side effects	∅	No data available

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

b) adults with asthma who are not adequately controlled with high-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	∅	No data available
Side effects	↔	No relevant difference for the benefit assessment. There are no assessable data for SAE.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

TRIGGER study: BDP/Form/Glyc **vs** BDP/Form + Tio

Mortality

Endpoint	BDP/Form/Glyc		BDP/Form + Tio		BDP/Form/Glyc vs BDP/Form + Tio
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI]; p-value[a]
Overall mortality					
	571	1 (0.2)	287	0 (0)	1.51 [0.06; 36.96]; 0.573

Morbidity

Endpoint	BDP/Form/Glyc			BDP/Form + Tio			BDP/Form/Glyc vs BDP/Form + Tio
	N	Adjusted annual rate [95% CI][b]		N	Adjusted annual rate [95% CI][b]		Rate ratio [95 % CI]; p-value[b]
severe asthma exacerbations[c]							
	571	1 (0.2)		287	0 (0)		1.51 [0.06; 36.96]; 0.573
	N	Patients with event n (%)		N	Patients with event n (%)		RR [95 % CI]; p-value[a]
severe asthma exacerbations[c] *(presented additionally)*							
	571	119 (20.8)		287	47 (16.4)		1.27 [0.94; 1.73]; 0.128
	N[d]	Values at start of study MV (SD)	Change MV [95% CI]	N[d]	Values at start of study MV (SD)	Change MV [95% CI]	MD RR [95% CI]; p-value
Proportion of asthma symptom-free days[e] (%)							
	571	10.16 (23.09)	16.57 [14.30; 18.84][f]	287	10.78 (26.58)	12.73 [9.51; 15.94][f]	3.84 [-0.09; 7.78]; 0.055[f]
Health status (EQ-5D VAS[e])							
	535	67.20 (13.51)	9.49 [8.47; 10.51][g]	263	68.37 (14.31)	8.83 [7.38; 10.27][g]	0.66 [-1.11; 2.43]; 0.464[g]

Health-related quality of life

No data collected.

Side effects

Endpoint	BDP/Form/Glyc		BDP/Form + Tio		BDP/Form/Glyc vs BDP/Form + Tio
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p-value[a]
Adverse events *(presented additionally)*					
	571	410 (71.8)	287	210 (73.2)	-
Serious adverse events (SAE)					
	571	no usable data available[h]	287	no usable data available[h]	
Therapy discontinuation due to adverse events					
	571	4 (0.7)	287	2 (0.7)	1.01 [0.19; 5.46]; > 0.999
MACE[i]					
	571	3 (0.5)	287	0 (0)	3.52 [0.18; 68.00]; 0.268

a. own calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to Martín Andrés & Silva Mato, 1994]). In the case of 0 events in a study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.

b. *adjusted annual rates with CI (per treatment group) and rate ratio with CI and p-value (group comparison): presumptive negative-binomial regression with the variables treatment, region and number of asthma exacerbations in the previous year as well as logarithmised time the patient was in the study as offset*

c. Defined as a deterioration of asthma symptoms that required treatment with systemic corticosteroids for at least three days.

d. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the valuesat the start of study can be based on other patient numbers.

e. Higher (increasing) values mean a higher percentage of symptom-free days and better health status; positive effects (intervention minus control) mean an advantage for the intervention.

f. MV with CI (mean change over the course of the study per treatment group) and MD with CI and p-value: MMRM with the variables treatment, time between visits, region and value of run-in phase, and the interactions treatment x time between visits and value of run-in phase x time between visits; effect refers to the changes averaged over the course of the study between the respective time between visits and run-in phase

g. MV with CI (change in end of study per treatment group) and MD with CI and p-value: MMRM with the variables treatment, visits, region and value at baseline as well as the interactions treatment x visit and value at baseline x visit; effect refers to the difference between study end and baseline

h. no usable data, as a relevant proportion of events are recorded for PT "asthma".

i. The following AE were considered: acute myocardial infarction (acute coronary syndrome, non-fatal myocardial infarction), stroke (non-fatal stroke), death due to a cardiovascular event (cardiac arrest, sudden death), arrhythmia (sustained supraventricular and sustained ventricular), cardiac insufficiency.

Abbreviations used:
BDP: beclometasone; Form: formoterol; Glyc: glycopyrronium; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; CI: confidence interval; n: number of patients with (at least 1) event; MACE: major adverse cardiovascular event; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; N: number of patients evaluated; PT: preferred term; RR: relative risk; SD: standard deviation; SAE: serious adverse event; Tio: tiotropium; AE: adverse event; VAS: visual analogue scale; vs = versus

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

a) adults with asthma who are not adequately controlled with medium-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

b) adults with asthma who are not adequately controlled with high-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

approx. 290,000 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 Trimbow (active ingredient: beclometasone/formoterol/glycopyrronium) at the following publicly accessible link (last access: 19 May 2021):
https://www.ema.europa.eu/en/documents/product-information/trimbow-epar-product-information_de.pdf

4. Treatment costs

Annual treatment costs:

a) Adults with asthma who are not adequately controlled with medium-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Beclometasone/formoterol/glycopyrronium 87 µg/5 µg/9 µg	€ 1022.97
Appropriate comparator therapy:	
A patient-individual therapy escalation taking into account the previous therapy, the severity of the disease and the symptomatology under selection of:	
Medium-dose ICS and LABA and LAMA	
Inhaled corticosteroids (ICS, medium-dose)	
Ciclesonide	€ 95.63
Long-acting beta-2-adrenergic agonists (LABA)	
Formoterol	€ 309.07

Designation of the therapy	Annual treatment costs/ patient
ICS/LABA fixed combinations (medium dose)	
Salmeterol/ fluticasone	€ 241.63 - € 369.95
Long-acting muscarinic receptor antagonists (LAMA)	
Tiotropium	€ 752.27
OR	
high-dose ICS and LABA	
Inhaled synthetic corticosteroids (ICS, high dose)	
Budesonide	€ 140.31
long-acting beta-2-adrenergic agonists (LABA)	
Formoterol	€ 309.07
ICS/LABA fixed combinations (high dose)	
Salmeterol/ fluticasone	€ 495.51

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 July 2021)

b) Adults with asthma who are not adequately controlled with high-dose ICS/LABA therapy and who have experienced at least one asthma exacerbation in the previous year

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Beclometasone/formoterol/glycopyrronium 172 µg/5 µg/9 µg	Costs not comprehensible, package price not to be found in LAUER-TAXE®
Appropriate comparator therapy:	
High-dose ICS and LABA and LAMA	
Inhaled synthetic corticosteroids (ICS, high dose)	
Budesonide	€ 140.31
Long-acting beta-2-adrenergic agonists (LABA)	
Formoterol	€ 309.07
ICS/LABA fixed combinations (high dose)	
Salmeterol/ fluticasone	€ 495.51
Long-acting muscarinic receptor antagonists (LAMA)	
Tiotropium	€ 752.27
ICS/LABA/ LAMA fixed combinations (high dose)	
Indacaterol/ glycopyrronium/ mometasone	€ 1,131.82

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 July 2021)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 5 August 2021.

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

Berlin, 5 August 2021

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

Prof. Hecken