Resolution

Gemeinsamer Bundesausschuss

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 Indacaterol Acetate/Glycopyrronium Bromide/Mometasone Furoate (Asthma)

of 4 February 2021

At its session on 4 February 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), amended by the announcement 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 combination indacaterol acetate/glycopyrronium bromide/mometasone furoate as follows:

Indacaterol acetate/glycopyrronium bromide/mometasone furoate

Resolution of: 4 February 2021
Entry into force on: 4 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 3 July 2020):

Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

Therapeutic indication of the resolution (resolution of 4 February 2021):

See therapeutic indication according to marketing authorisation

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

Adult patients with asthma who are not adequately controlled with a maintenance combination of a LABA and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year

Appropriate comparator therapy:

High-dose ICS and LABA and LAMA

Extent and probability of the additional benefit of indacaterol acetate/glycopyrronium bromide/mometasone furoate compared with salmeterol/fluticasone + tiotropium

An additional benefit is not proven.

Study results according to endpoints:[1]

Adult patients with asthma who are not adequately controlled with a maintenance combination of a LABA and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↔	No differences relevant for the benefit assessment.
Health-related quality of life	↔	No differences relevant for the benefit assessment.

[1] Data from the dossier assessment of the IQWiG (A20-69) and the addendum (A20-125) unless otherwise indicated.

Endpoint category	Direction of effect/ Risk of bias	Summary
Side effects	↔	No differences relevant for the benefit assessment.

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

ARGON study[2]: Indacaterol/glycopyrronium/mometasone vs salmeterol/fluticasone + tiotropium

Mortality

Endpoint	Ind/Glyc/Mom		Sal/Flu + Tio		Ind/Glyc/Mom vs Sal/Flu + Tio
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*
Mortality					
	242	0 (0)	232	1 (0.4)	0.32 [0.01; 7.81]; 0.484

Morbidity

Endpoint	Ind/Glyc/Mom		Sal/Flu + Tio		Ind/Glyc/Mom vs Sal/Flu + Tio
	N	*Mean annual rate [95% CI][c]*	*N*	*Mean annual rate [95% CI][c]*	*Rate ratio [95% CI]; p value[c]*
Severe asthma exacerbations[a]					
	242	0.49 [0.36; 0.68]	232	0.34 [0.23; 0.49]	1.46 [0.91; 2.35]; 0.121
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*

[2] Relevant sub-population from the ARGON study: Patients previously treated with a combination of a LABA and a high dose of an inhaled corticosteroid.

Endpoint	Ind/Glyc/Mom			Sal/Flu + Tio			Ind/Glyc/Mom vs Sal/Flu + Tio
Severe asthma exacerbations[a] *(presented additionally)*							
	242	43 (17.8)		232	28 (12.1)		1.47 [0.95; 2.29]; 0.084[b]
	N	*Values at start of study MV (SD)*	*Change at week 24 MV[d] (SE)*	*N*	*Values at start of study MV (SD)*	*Change at week 24 MV[d] (SE)*	*MD [95% CI]; p value[d]*
Asthma symptomatology							
ACQ-5[e]	232	2.59 (0.60)	−1.25 (0.08)	219	2.52 (0.57)	−1.24 (0.09)	−0.01 [−0.17; 0.16]; 0.926

a. Definition: Deterioration of asthma symptoms (e,g, shortness of breath, cough, wheezing, and chest tightness) that required an administration or increase of OCS for ≥ 3 consecutive days and/or admission to an emergency department (or local equivalent structure) and/or hospitalisation because of asthma and/or death because of asthma.
b. IQWiG calculation of RR, CI (asymptotic), and p value (unconditional exact test, CSZ method according to Martín Andrés & Silva Mato, 1994).
c. Mean rates with CI (per treatment group) as well as rate ratio with CI and p value (group comparison): negative-binomial regression with the variables treatment, region, and history of exacerbations as well as the offset variable log(exposure).
d. MV and SE (change at Week 24 per treatment group) as well as MD and p value (group comparison): MMRM with the variables treatment, region, round, and value at start of study as well as the interactions value at start of study×visit and treatment×visit.
e. The ACQ-5 assesses symptomatology on a scale from 0 to 6. Lower (decreasing) values mean better symptomatology; negative statistically significant effects (intervention minus control) mean an advantage for Ind/Glyc/Mom.

Health-related quality of life

Endpoint	Ind/Glyc/Mom			Sal/Flu + Tio			Ind/Glyc/Mom vs Sal/Flu + Tio
Asthma Quality of Life Questionnaire (AQLQ-S)							
	N	*Values at start of study MV (SD)*	*Change at week 24 MV[a] (SE)*	N	*Values at start of study MV (SD)*	*Change at week 24 MV[a] (SE)*	*MD [95% CI]; p value[a]*
AQLQ-S total score[b]	231	4.69 (0.86)	0.74 (0.08)	215	4.71 (0.88)	0.74 (0.08)	0.00 [−0.15; 0.16]; 0.957
	N	*Patients with event n (%)*		*N*	*Patients with event n (%)*		*RR [95% CI]; p value*

Endpoint	Ind/Glyc/Mom		Sal/Flu + Tio		Ind/Glyc/Mom vs Sal/Flu + Tio
AQLQ-S responder (increase by ≥ 0.5 points)	231	163 (70.6)	215	140 (65.1)	1.11 [0.97; 1.27]; 0.113[c]
St. George's Respiratory Questionnaire (SGRQ)					
	N	*Values at start of study MV (SD)*	*Change at week 24 MV[a] (SE)*	N	*Values at start of study MV (SD)*	*Change at week 24 MV[a] (SE)*	*MD [95% CI]; p value[a]*
SGRQ total score[d]	228	39.86 (16.08)	−11.85 (1.64)	211	38.51 (17.27)	−10.19 (1.68)	−1.66 [−4.64; 1.31]; 0.273
	N	*Patients with event n (%)*		*N*	*Patients with event n (%)*		*RR [95% CI]; p value*
SGRQ responder reduction by ≥ 4 points	240	158 (65.8)		224	129 (57.6)		1.14 [0.99; 1.32]; 0.070

a. MV and SE (change at Week 24 per treatment group) as well as MD and p value (group comparison); for the AQLQ-S instrument: MMRM with the variables treatment, region, round, and value at start of study as well as the interactions value at start of study×visit and treatment×visit; for the SGRQ instrument: ANCOVA with the variables treatment, region, and value at start of study
b. Higher (increasing) values mean better health-related quality of life; positive statistically significant effects (intervention minus control) mean an advantage for Ind/Glyc/Mom.
c. RR with CI and p value: Poisson regression with the variables treatment, round, region, and value at start of study as well as the interactions value at start of study×visit and treatment×visit.
d. Lower (decreasing) values mean better health-related quality of life; negative statistically significant effects (intervention minus control) mean an advantage for Ind/Glyc/Mom.

Side effects

Endpoint	Ind/Glyc/Mom		Sal/Flu + Tio		Ind/Glyc/Mom vs Sal/Flu + Tio
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*
Total adverse events *(presented additionally)*[a]					
	242	126 (52.1)	232	107 (46.1)	-
Serious adverse events (SAE)[a]					
	242	9 (3.7)	232	10 (4.3)	0.86 [0.36; 2.09]; 0.743
Therapy discontinuations because of adverse events					

Endpoint	Ind/Glyc/Mom		Sal/Flu + Tio		Ind/Glyc/Mom vs Sal/Flu + Tio
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*RR [95% CI] p value*
	242	1 (0.4)	232	3 (1.3)	0.32 [0.03; 3.05]; 0.322

a. without the PT "Asthma".

Abbreviations:
ACQ: Asthma Control Questionnaire; ANCOVA: analysis of covariance; AQLQ-S: standardised Asthma Quality of Life Questionnaire; Flu: fluticasone; Glyc: glycopyrronium bromide; Ind: indacaterol acetate; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measurements; Mom: mometasone furoate; MV: mean value; n: number of patients with (at least 1) event, N: number of patients evaluated; PT: preferred term; RR: relative risk; Sal: salmeterol; SD: standard deviation; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; SAE: serious adverse event; Tio: tiotropium; AE: adverse event

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

Adult patients with asthma who are not adequately controlled with a maintenance combination of a LABA and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year

approx. 100,000 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 Enerzair Breezhaler (active ingredient combination: indacaterol acetate/glycopyrronium bromide/mometasone furoate) at the following publicly accessible link (last access: 21 January 2021):
https://www.ema.europa.eu/documents/product-information/enerzair-breezhaler-epar-product-information_de.pdf

4. Treatment costs

Annual treatment costs:

Adult patients with asthma who are not adequately controlled with a maintenance combination of a LABA and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Indacaterol acetate/glycopyrronium bromide/mometasone furoate	€ 1,131.82

Designation of the therapy	Annual treatment costs/patient
Appropriate comparator therapy:	
Inhaled corticosteroids (ICS, high-dose)	
Budesonide	€ 140.32
Long-acting beta-2 sympathomimetics (LABA)	
Formoterol	€ 309.08
ICS/LABA fixed combinations (high-dose)	
Fluticasone/salmeterol	€ 495.52
Long-acting muscarinic antagonists (LAMA)	
Tiotropium	€ 752.27

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

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 4 February 2021.

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

Berlin, 4 February 2021

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

Prof. Hecken