Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-L):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Baloxavir marboxil (Influenza, ≥ 12 years)

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 baloxavir marboxil as follows:

Baloxavir marboxil

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

Therapeutic indication (according to the marketing authorisation of 7 January 2021):

Treatment of influenza: Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 12 years and above.

Post-exposure prophylaxis of influenza: Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 12 years and above.

Xofluza should be used in accordance with official recommendations.

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

Xofluza is indicated for the treatment of uncomplicated influenza in adults and adolescents aged 12 years and above.

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

a) adults and adolescents aged 12 years and above with influenza without risk of influenza-related complications:

Appropriate comparator therapy:

symptomatic therapy (antipyretics, antiphlogistics, analgesics)

Extent and probability of the additional benefit of baloxavir marboxil compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) adults and adolescents aged 12 years and above with influenza if there is an increased risk of a severe course::

Appropriate comparator therapy:

antiviral therapy (oseltamivir or zanamivir)

Extent and likelihood of additional benefit of baloxavir marboxil over oseltamivir:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) adults and adolescents aged 12 years and above with influenza without risk of influenza-related complications

No adequate data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	There are no data.
Side effects	n.a.	There are no assessable data.
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 and adolescents aged 12 years and above with influenza, when there is an increased risk of a severe course of the disease

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	n.a.	No assessable data are available for the relevant overall population; no differences relevant to the benefit assessment are available for those with positive influenza (presented additionally).
Health-related quality of life	∅	There are no data.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-21) unless otherwise indicated.

Side effects	↔	No relevant difference 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

CAPSTONE-2 study: double-blind RCT (baloxavir marboxil **vs** oseltamivir **vs** placebo); 14-day observation

Mortality

Endpoint CAPSTONE-2 study	**Baloxavir marboxil**		**Oseltamivir**		**Baloxavir marboxil vs oseltamivir**
	N	Subjects with event n (%)	N	Subjects with event n (%)	RR [95% CI] p-value[a]
Overall mortality	730	0 (0)	721	1 (0.1)	033 [0.01; 8.07][b]; 0.370

Morbidity

Results are only available for the ITTI population with positive influenza detection by RT-PCR for the endpoint category morbidity; the results are presented below additionally.
For the total population relevant to the evaluation, for which no data were submitted, a change in the effect in the direction of zero effect can be assumed compared to the effect in the ITTI population shown.

Endpoint CAPSTONE-2 study	**Baloxavir marboxil**		**Oseltamivir**		**Baloxavir marboxil vs oseltamivir**
	N	Subjects with event n (%)	N	Subjects with event n (%)	RR [95% CI] p-value[a]
influenza-typical complications[c] *(presented additionally)*	388	11 (2.8)	389	18 (4.6)	0.61 [0.29; 1.28]; 0.247
	N	Median time to event in months [95 % CI] Subjects with event n (%)	N	Median time to event in months [95 % CI] Subjects with event n (%)	HR [95% CI] p-value
Influenza symptomatology[d]	385	73.2 [67.2; 85.1]	388	81.0 [69.4; 91.5]	1.02 [0.87; 1.18]; 0.845

(presented additionally)		343 (89.1)			341 (87.9)		
	N	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	N	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	RR [95% CI] p-value[a]
Health status (EQ-5D VAS) *(presented additionally)*	376	n.d.	40.22 (0.51)	379	n.d.	40.38 (0.51)	-0.16 [-1.07; 0.75]; 0.730

Health-related quality of life

Health-related quality of life
Quality of life was not recorded in the CAPSTONE-2 study.

Side effects

Endpoint CAPSTONE-2 study	**Baloxavir marboxil**		**Oseltamivir**		**Baloxavir marboxil vs oseltamivir**
	N	Subjects with event n (%)	N	Subjects with event n (%)	RR [95% CI] p-value[a]
Adverse events (AE) in total					
AEs (presented additionally)	730	179 (24.5)	721	192 (26.6)	-
Serious adverse events (SAE)					
SAEs	730	5 (0.7)	721	8 (1.1)	0.62 [0.20; 1.88]; 0.530
Therapy discontinuation due to adverse events					
Discontinuation because of AEs	730	5 (0.7)	721	4 (0.6)	1.23 [0.33; 4.58]; 0.828

a. own calculation: exact unconditional test (CSZ method)
b. own calculation of RR and CI (asymptotic); because no events occurred in the baloxavir marboxil arm, the correction term 0.5 was used in the calculation in both study arms.
c. include death, hospitalisation, sinusitis, bronchitis, otitis media, and radiologically confirmed pneumonia
d. Time to improvement of all influenza symptoms. Patient-reported symptoms include cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue.

Abbreviations used: EQ-5D VAS: European Quality of Life Questionnaire 5 Dimensions - visual analogue scale; HR: hazard ratio; ITTI: Intention to treat infected; CI: confidence interval; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; RCT: randomised controlled trial; RR: relative risk; RT-PCR: reverse transcriptase-polymerase chain reaction; SD: standard deviation; SAE: serious adverse event; AE: adverse event; vs: versus.

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

a) Adults and adolescents aged 12 years and above with influenza without risk of influenza-related complications

approx. 1,091,000 to 1,925,000 patients

b) Adults and adolescents aged 12 years and above with influenza, when there is an increased risk of a severe course of the disease

approx. 780,000 to 1,378,000 patients

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

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 Xofluza (active ingredient: baloxavir marboxil) at the following publicly accessible link (last access: 15 July 2021): https://www.ema.europa.eu/en/documents/product-information/xofluza-epar-product-information_de.pdf

4. Treatment costs

a) adults and adolescents aged 12 years and above with influenza without risk of influenza-related complications

Designation of the therapy	Treatment costs/ subject
Medicinal product to be assessed:	
Baloxavir marboxil[2]	€ 109.60 – € 209.92
Appropriate comparator therapy:	
Symptomatic therapy	patient-individual

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

Costs for additionally required SHI services: not applicable

b) adults and adolescents aged 12 years and above with influenza, when there is an increased risk of a severe course of the disease

Designation of the therapy	Treatment costs/ subject
Medicinal product to be assessed:	

[2]The range of baloxavir marboxil is based on different doses depending on body weight (< 80 kg bw or ≥ 80 kg bw, respectively)

Designation of the therapy	Treatment costs/ subject
Baloxavir marboxil[2]	€ 109.60 – € 209.92
Appropriate comparator therapy:	
Oseltamivir	€ 28.40
Zanamivir	€ 32.21

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