Gemeinsamer Bundesausschuss

Justification

of the 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 Baloxavir marboxil (Influenza, post-exposure prophylaxis, ≥ 12 years)

of 5 August 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient baloxavir marboxil in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 February 2021. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 February 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 17 May 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of baloxavir marboxil compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the

IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of baloxavir marboxil.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of baloxavir marboxil (Xofluza) according to product information

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 post-exposure prophylaxis of influenza in individuals aged 12 years and above.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for post-exposure prophylaxis was determined as follows:

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

   monitoring wait-and-see approach

b) adults and adolescents 12 years of age and above with influenza exposure at risk for influenza-related complications

   antiviral therapy (oseltamivir or zanamivir)

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

[1] General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The following medicinal products are approved for the treatment of post-exposure prophylaxis of influenza infection: Neuraminidase inhibitors: oseltamivir, zanamivir

on 2. Non-medicinal treatments are not considered for the therapeutic indication.

on 3. There are no resolutions of the G-BA on an amendment of the AM-RL: Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication.

on 4. The general state of medical knowledge was illustrated by a systematic search for guidelines and reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V".

The antiviral active ingredients oseltamivir and zanamivir are approved for post-exposure prophylaxis of influenza. Evidence for these active ingredients is available in a systematic review and a guideline. The recommendations of the Robert Koch Institute on post-exposure prophylaxis[2] also advocate the use of antiviral active ingredients only in subjects with an increased risk of a severe course of influenza. Therefore, based on the available evidence and the recommendations, the RKI, monitoring wait-and-see approach is determined as the appropriate comparator therapy for subjects with influenza exposure without risk of influenza-related complications.

For subjects with influenza exposure and an increased risk of a severe course, antiviral therapy with oseltamivir or zanamivir is determined to be appropriate. Antiviral medicinal products for post-exposure prophylaxis of influenza are generally not a substitute for influenza vaccination. The appropriate use should be decided on a case-by-case basis, taking into account the circumstances and the population group to be protected. The use of antiviral active ingredients for post-exposure prophylaxis of influenza should take into account official recommendations, epidemiological variability and the impact of the disease in different geographical regions and patient populations.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

[2] https://www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Influenza_saisonal.html

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of baloxavir marboxil is assessed as follows:

a) For adults and adolescents 12 years of age and above with influenza exposure and no risk of influenza-related complications, there is an indication of a considerable additional benefit for baloxavir marboxil compared with the monitoring wait-and-see approach.

b) For adults and adolescents 12 years of age and above with influenza exposure at risk for influenza-related complications, an additional benefit of baloxavir marboxil compared with the appropriate comparator therapy is not proven.

Justification for patient group a):

The BLOCKSTONE study is available to assess the additional benefit of baloxavir marboxil for post-exposure prophylaxis in adults and adolescents aged 12 years and above with influenza without risk of influenza-related complications.

The BLOCKSTONE study is a randomised, double-blind, placebo-controlled trial (RCT) comparing baloxavir marboxil with placebo conducted exclusively in Japan. In the study, only adults and children with contact with an influenza-ill subject in their own household (index subject) who tested positive for influenza virus by rapid test and whose first rise in body temperature to ≥ 37.5°C began no more than 48 hours before signing the informed consent form were studied. A total of 545 index subjects were included in the study. The subjects studied lived with the index subject in the same household for at least 48 hours prior to informed consent and beyond that for at least an additional 10 days of the study (follow-up period). No influenza symptoms such as fever or cough were allowed at the time of enrolment. Subjects were assigned randomly to the intervention arm (n = 375) and the comparator arm (n = 377) and stratified based on "time from onset of influenza virus infection of the index subject to informed consent" (< 24 hours, ≥ 24 hours), treatment of the index subject (baloxavir marboxil, other drugs), and age of the subjects (< 12 years, ≥ 12 years). The study's primary endpoint is symptomatic influenza (fever and respiratory symptom) confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR). In addition, further patient-relevant endpoints on morbidity and side effects were collected.

The study also included individuals < 12 years of age and those at risk for influenza-related complications. The assessment on the patient group a) refers to individuals without risk of influenza-related complications ≥ 12 years. Therefore, only the results from the sub-population ≥ 12 years of age and at no risk for influenza-related complications will be used. A total of 549 individuals correspond to the relevant sub-population, of which 275 individuals were in the intervention arm, and 274 individuals were in the comparator arm.

Mortality

In the BLOCKSTONE study, no statistically significant difference was determined between the treatment groups for the endpoint overall survival.

Morbidity

The endpoint of symptomatic influenza infection was operationalised as fever or at least one other influenza symptom (cough, sore throat, nasal discharge/nasal congestion, headache, chills,

muscle or joint pain, or fatigue) plus an additional positive RT-PCR test. Both the evaluation of the total population and the supplementary evaluation on the proportion of individuals with positive RT-PCR test for influenza regardless of symptoms were presented.

The follow-up of these morbidity endpoints was 10 days, which is considered to be sufficiently long in the present therapeutic indication since the infectivity is on average 4 to 5 days after symptom onset and the incubation period is on average 1 to 2 days. If infection occurred during the selected observation period, it is assumed that influenza infection also occurred in the study subjects.

In the endpoint symptomatic influenza infection and thus in the overall view of the morbidity category, a statistically significant difference to the advantage of baloxavir marboxil over the monitoring wait-and-see approach was shown in both selected evaluations.

Quality of life

The endpoint health-related quality of life was not collected in the BLOCKSTONE study.

Side effects

There was no statistically significant difference between the treatment groups for the endpoints serious adverse events (SAE) and discontinuation due to AEs.

A summary of the results shows no difference between baloxavir marboxil and the monitoring wait-and-see approach in the side effect category.

Overall assessment / conclusion

The double-blind, randomised controlled study BLOCKSTONE was submitted to assess the extent of additional benefit of baloxavir marboxil. Results on mortality, morbidity and side effects are available. There was no assessment of the health-related quality of life in the study.

There was no statistically significant difference between baloxavir marboxil versus the monitoring wait-and-see approach for the endpoint overall survival.
The overall results for the category morbidity for the endpoint of symptomatic influenza infection showed a statistically significant difference in the benefit of baloxavir marboxil compared to the monitoring wait-and-see approach.
There was no statistically significant difference between baloxavir marboxil versus monitoring wait-and-see approach in the overall observation of the endpoints from category side effects for the endpoints serious adverse events (SAEs) and discontinuation due to AEs.

In summary, for adults and adolescents 12 years of age and above with influenza exposure and no risk of influenza-related complications, the overall results for mortality, morbidity, and side effects indicate a considerable additional benefit of baloxavir marboxil compared with the monitoring wait-and-see approach.

Reliability of data (probability of additional benefit)

This evaluation is based on the results of the RCT BLOCKSTONE in adults and adolescents 12 years of age and above with influenza exposure without risk of influenza-related complications. Even though the BLOCKSTONE study only included subjects of Asian descent, it can be assumed that the effects observed in the Japanese study population of the BLOCKSTONE study can also be transferred to subjects of non-Asian descent with sufficient certainty.
Since the present benefit assessment is based on the results of only one included study, only indications of an additional benefit can be derived with regard to the reliability of data. The

risk of bias of all included endpoints with appropriate operationalisation is rated as low. The reliability of data for the additional benefit determined is classified in the category "indication".

Justification for patient group b):

For the patient group "adults and adolescents aged 12 years and above with influenza exposure without risk of influenza-related complications", no study was submitted by the pharmaceutical company that would have been suitable for the assessment of the additional benefit of baloxavir marboxil in the present therapeutic indication compared to the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Xofluza with the active ingredient baloxavir marboxil. The therapeutic indication assessed here is as follows: For post-exposure prophylaxis of influenza in adults and adolescents 12 years of age and above.

In the therapeutic indication to be considered, two patient groups were distinguished:

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

b) adults and adolescents 12 years of age and above with influenza exposure at risk for influenza-related complications

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

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the double-blind RCT BLOCKSTONE (baloxavir marboxil vs placebo), which examines subjects with contact to an influenza-ill subject in their own household (index subject).

In the study's overall results, there was a statistically significant difference in the endpoint of symptomatic influenza infection in the morbidity category in favour of baloxavir marboxil compared with the monitoring wait-and-see approach.

In the endpoint mortality and side effects, there was no statistically significant difference between the two treatment groups.

In summary, for adults and adolescents 12 years of age and above with influenza exposure and no risk of influenza-related complications, there is an indication of a considerable additional benefit for baloxavir marboxil compared with the monitoring wait-and-see approach.

b) adults and adolescents 12 years of age and above with influenza exposure at risk for influenza-related complications

The G-BA determined an antiviral therapy (oseltamivir and zanamivir) as an appropriate comparator therapy.

For this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of baloxavir marboxil compared with the appropriate comparator therapy.

Overall, for adults and adolescents 12 years of age and above with influenza exposure at risk for influenza-related complications, an additional benefit of baloxavir marboxil compared with the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The data on the number of patients without risk of influenza-related complications (approx. 1,113,000 - 2,291,000) and with increased risk of a severe course (approx. 796,000 - 1,640,000) refer to the target population in the statutory health insurance (SHI).

The information follows the representations of the pharmaceutical company. Uncertainty exists in equating the number of excess consultations with the number of influenza cases, as these are only consultations that exceed the expected level during the influenza wave of the respective season, thus excluding influenza-related consultations outside influenza waves and influenza cases without consultation. Since only subjects who would become infected through contact with a subject with influenza are considered, subjects who have had close contact with a subject with confirmed or suspected influenza but do not become infected are not considered. In addition, the exclusion of pregnant patients is unclear, as this restriction of use is only recommended as a precautionary measure in the product information. Furthermore, it is unclear how accurately the pharmaceutical entrepreneur's operationalisation (presence of chronic diseases and/or age 65 years and above) reflects a risk for influenza-related complications.

2.3 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 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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2021).

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

If no maximum treatment duration is specified in the product information, the regular duration of antiviral therapy is assumed as the duration of treatment. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information. The calculation of the annual treatment costs was based on the assumption that a patient only receives one antiviral therapy for post-exposure prophylaxis per year or per season; therefore, further treatments due to exposure are not reflected in the annual treatment costs.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Days of treatment/ subject/ year
Medicinal product to be assessed				
Baloxavir marboxil	Single-dose	1	1	1
Appropriate comparator therapy				
Patient population a)				
Monitoring wait-and-see approach	incalculable			
Patient population b)				
Oseltamivir	1 x daily for 10 days	10	1	10
Zanamivir	1 x daily 2 inhalations (equivalent to 1 x daily 2 x 5 mg) for 10 days	10	1	10

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ subject/ days of treatment	Usage by potency/ day of treatment	Treatment days/ subject/ year	Average consumption by potency
Medicinal product to be assessed					
Baloxavir marboxil	< 80 kg: 40 mg	40 mg	2 x 20 mg	1	2 x 20 mg
	≥ 80 kg: 80 mg	80 mg	2 x 40 mg	1	2 x 40 mg
Appropriate comparator therapy					
Patient population a)					
Monitoring wait-and-see approach	incalculable				
Patient population b)					
Oseltamivir	1 x 75 mg	75 mg	1 x 75 mg	10	10 x 75 mg
Zanamivir	1 x 10 mg	10 mg	2 x 5 mg	10	20 x 5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both based on the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. I To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Baloxavir marboxil 20 mg	2 FCT	€ 117.25	€ 1.77	€ 5.88	€ 109.60
Baloxavir marboxil 40 mg	2 FCT	€ 223.45	€ 1.77	€ 11.76	€ 209.92
Appropriate comparator therapy					
Monitoring wait-and-see approach	incalculable				
Oseltamivir	10 HC	€ 31.12	€ 1.77	€ 0.95	€ 28.40
Zanamivir	4 x 5 mg POW	€ 35.32	€ 1.77	€ 1.34	€ 32.21
FCT: Film-coated tablets; HC: Hard capsule; POW: Powder					

LAUER-TAXE® last revised: 15 July 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additional required SHI services had to be considered account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 21 April 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of baloxavir marboxil to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 12 February 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient baloxavir marboxil.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 May 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 17 May 2021. The deadline for submitting written statements was 7 June 2021.

The oral hearing was held on 21 June 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the subcommittee session on 27 July 2021, and the proposed resolution was approved.

At its session on 5 August 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 April 2020	Determination of the appropriate comparator therapy
Working group Section 35a	16 June 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	21 June 2021	Conduct of the oral hearing
Working group Section 35a	30 June 2021 13 July 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	27 July 2021	Concluding consultation of the draft resolution
Plenum	5 August 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 August 2021

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

Prof. Hecken