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, ≥ 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 05.08.2021):

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

symptomatic therapy (antipyretics, antiphlogistics, analgesics)

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

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.

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

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. 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 virustatic medicinal products are approved for the treatment of influenza infection: Neuraminidase inhibitors (oseltamivir, zanamivir) and amantadine (approved exclusively for influenza A infection).

In addition, antipyretic, antiphlogistic and analgesic active ingredients are available for the treatment of influenza-related symptoms.

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 treatment of influenza infections focuses on symptomatic therapy of influenza-related symptoms. Symptomatic therapy includes antipyretic, antiphlogistic and analgesic measures. In addition, evidence for the approved antiviral active ingredients oseltamivir and zanamivir is available in the form of three systematic reviews and one guideline. According to the recommendation of the Robert Koch Institute[2], the use of one of these antiviral therapies should be considered if there is an increased risk of a severe course. No aggregated evidence in the form of systematic reviews is available for the antiviral active ingredient amantadine; moreover, it currently plays no role in everyday health care and is therefore not included in the appropriate comparator therapy.

Based on the available evidence and the recommendations of the RKI for the therapy of influenza, symptomatic therapy is determined as appropriate comparator therapy for ill subjects without risk of influenza-related complications: e.g. fever reduction or pain therapy (e.g. antipyretics, antiphlogistics, analgesics). It is assumed that supportive measures (e.g. sufficient hydration) and symptomatic concomitant therapy (e.g. antipyretics, antiphlogistics, analgesics) will be implemented in both study arms. These measures shall be documented and presented in the dossier.

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

For ill subjects with an increased risk of a severe course, antiviral therapy with oseltamivir or zanamivir is determined to be appropriate. Therapy with antiviral medicinal products should be started as early as possible within the first two days after the onset of symptoms of influenza, in accordance with the marketing authorisation. Official recommendations, epidemiological variability, and the impact of the disease in different geographic regions and patient populations should be considered.

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

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 aged 12 years and above with influenza without risk of influenza-related complications, the additional benefit of baloxavir marboxil compared with the appropriate comparator therapy is not proven.

b) For adults and adolescents aged 12 years and above with influenza, when there is an increased risk of a severe course of the disease, the additional benefit of baloxavir marboxil compared with oseltamivir is not proven.

Justification for patient group (a):

The two double-blind, randomised controlled trials (RCT) JapicCTI-153090 and CAPSTONE-1 are available to assess the additional benefit of baloxavir marboxil for the treatment of adults and adolescents aged 12 years and above with influenza without risk of influenza-related complications.

JapicCTI-153090

The JapicCTI-153090 study is a double-blind RCT comparing baloxavir marboxil to placebo that enrolled 400 subjects aged ≥ 20 to < 65 years with antigen-confirmed influenza who were also required to have a fever and at least one other general and respiratory symptom of influenza and no risk factors for influenza-related complications. Symptomatic therapy was not permitted except for the use of paracetamol as "rescue therapy" in cases of severe symptomatology. The primary endpoint of the study was time to the improvement of influenza symptoms. Patient-relevant additional endpoints were endpoints regarding symptomatology, health status, and adverse events (AEs). The duration of the study was 22 days.

CAPSTONE-1

The multicentre, double-blind RCT CAPSTONE-1 enrolled 1,436 subjects analogous to the JapicCTI-153090 study with symptomatically diagnosed influenza infection, aged 12 to ≤ 64 years, with no risk factors for influenza-related complications, and randomised 2:2:1 to the three study arms baloxavir marboxil (N = 612), placebo (N = 310), oseltamivir (N = 514) and aged 12-19 years randomised 2:1 to the two study arms (placebo, baloxavir marboxil). Symptomatic therapy was not allowed in the JapicCTI-153090 study, except for the use of paracetamol as "rescue therapy". The primary endpoint of the study was time to the improvement of influenza symptoms. Patient-relevant additional endpoints were endpoints

on symptomatology, health status and AEs. The treatment duration was five, and the study duration was 22 days.

To assess the side effects and mortality, respectively, the entire CAPSTONE-1 study population was evaluated (intention to treat [ITT] population), whereas to assess morbidity endpoints, the overall population was restricted to those with evidence of a positive influenza test by reverse transcriptase-polymerase chain reaction (RT-PCR) (intention to treat infected [ITTI] population).

Implementation of the appropriate comparator therapy

The G-BA determined symptomatic therapy (antipyretics, antiphlogistics, analgesics) to be the appropriate comparator therapy in this patient group. It is assumed that supportive measures (e.g. sufficient hydration) and symptomatic concomitant therapy (e.g. antipyretics, antiphlogistics, analgesics) will be implemented in both study arms.

In the JapicCTI-153090 and CAPSTONE-1 studies, symptomatic therapy with antipyretics and analgesics (with the exception of paracetamol) and other symptomatic therapies such as antitussives and expectorants or combination cold preparations were not allowed. Paracetamol was only allowed to be taken in cases where influenza symptoms such as fever, headache or muscle pain were so severe that subjects needed "rescue therapy". In the JapicCTI-153090 study, approximately 80% and in the CAPSTONE-1 study, approximately 5-7% in both study arms took paracetamol at least 1 time during the course of the study. Information on the frequency of taking is missing. Maximum dosage of 1,500 mg paracetamol per day was allowed in the JapicCTI-153090 study and 3,000 mg paracetamol per day in the CAPSTONE-1 study.

In both studies, the pharmaceutical company provided no sufficient justification for both the extreme differences in the frequency of the required rescue therapies and the different maximum daily doses allowed in the use of paracetamol. Overall, it is unclear how many subjects would have made use of symptomatic therapy for symptom relief and how frequently they would take it without the restriction described in the study protocol. Due to the restriction in the use of symptomatic therapy imposed by the study protocol, it is not possible to draw conclusions on the additional benefit in both studies for patient-relevant endpoints on influenza symptomatology and health status.

In summary, the limitation of therapeutic options for symptomatic treatment made in the studies does not seem appropriate. Due to the consequent uncertainties, 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. An additional benefit is not proven.

<u>Justification for patient group b):</u>

The double-blind, randomised controlled trial (RCT) CAPSTONE-2 is available to assess the additional benefit of baloxavir marboxil for the treatment of adults and adolescents aged 12 years and above with influenza when there is an increased risk of a severe course.

CAPSTONE-2

In the multicentre, double-blind RCT CAPSTONE-2 study, approximately 2,200 patients with symptomatically diagnosed influenza infection analogous to study CAPSTONE-1 and at least one risk factor for influenza-related complications aged 12 years and above were randomised 1:1:1 to three study arms (placebo, oseltamivir, and baloxavir marboxil). The placebo arm is

not relevant for the present benefit assessment. Subjects with a severe course at the time of enrolment were excluded. The study's primary endpoint was the time to the improvement of influenza symptoms (taking into account the change in pre-existing symptoms). Patient-relevant additional endpoints were endpoints on symptomatology, health status and AEs. The treatment duration is five days and the study period is 22 days.

Implementation of the appropriate comparator therapy

Even if antiviral therapy is used, as determined to be the appropriate comparator therapy, it is assumed that symptomatic therapy is also provided. In both study arms, additional supportive measures (e.g. sufficient hydration), as well as symptomatic concomitant therapy (e.g. antipyretics, antiphlogistics, analgesics), should be available.

In the CAPSTONE-2 study, analogous to the JapicCTI-153090 and CAPSTONE-1 studies, the use of antipyretics and analgesics, except for paracetamol, was not allowed as "rescue therapy" when influenza symptoms such as fever, headache, or muscle pain were severe enough that subjects needed them. The additional symptomatic concomitant therapy was therefore severely limited due to the restrictions according to the study protocol.

Study population - evaluation of the ITTI population

In the CAPSTONE-2 study, different evaluation populations are used for endpoints on morbidity and endpoints on side effects as well as mortality, analogous to the CAPSTONE-1 study. For the evaluation of side effects or mortality, the entire CAPSTONE-2 study population was evaluated (ITT population), while for the evaluation of morbidity endpoints, the total population was restricted to those with evidence of a positive influenza test by RT-PCR and who were enrolled in centres where Good Clinical Practice (GCP) standards were applied (ITTI population).

The evaluation of the total population without a regular influenza diagnosis confirmed by a PCR test reflects the conditions in health care since the diagnosis and subsequent treatment decision for antiviral treatment in clinical practice are generally not dependent on laboratory diagnostic evidence of influenza. In addition, according to the product information, no laboratory diagnostic evidence is required for the treatment of influenza with baloxavir marboxil. Accordingly, in the CAPSTONE-2 study, individuals were included and treated regardless of laboratory diagnostic evidence.

With the ITTI population, for the morbidity endpoints, only the data of those subjects are available in whom the infection with influenza viruses was confirmed by laboratory diagnostics afterwards, i.e. after the start of treatment. Since in the absence of viral infection - confirmed in this case by a negative RT-PCR test - an effect of the antiviral therapy cannot be assumed, the results of demonstrably ill influenza patients who have already been treated in advance can be presented additionally for the additional benefit assessment with regard to morbidity.

Mortality

In the CAPSTONE-2 study, for the endpoint overall survival there was no statistically significant difference between treatment groups.

Morbidity

For the endpoints influenza symptomatology, health status measured by the visual analogue scale of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D-VAS) and influenza-typical complications, no results are available for the relevant evaluation population (ITT population).

In the ITTI-population's side effects presented additionally, there were no statistically significant differences between the treatment groups in the morbidity endpoints considered. Compared to the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the evaluation.

Therefore, there is no difference between baloxavir marboxil and oseltamivir for the morbidity category in the synopsis of the results.

Quality of life

The endpoint health-related quality of life was not recorded in the CAPSTONE-2 study.

Side effects

For the endpoints serious adverse events (SAE) and discontinuation due to AEs, there was no statistically significant difference between baloxavir marboxil compared to oseltamivir.
A summary of the results shows no difference between baloxavir marboxil and oseltamivir in the category side effects.

Overall assessment

The double-blind, randomised controlled trial CAPSTONE-2 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.

Uncertainties arise for the study with regard to the additional symptomatic concomitant therapy available, which was severely limited due to the restrictions according to the study protocol.
For the endpoint overall survival, there was no statistically significant difference between baloxavir marboxil compared to oseltamivir.
In the overall morbidity category results for the endpoints influenza symptomatology, health status and influenza-typical complications, there was no statistically significant difference between baloxavir marboxil compared to oseltamivir in the supplementary ITTI-population presented additionally. Compared to the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the evaluation.
There was no statistically significant difference between baloxavir marboxil compared to oseltamivir in the overall category side effects for the endpoints serious adverse events (SAE) and discontinuation due to AEs.

In summary, for adults and adolescents aged 12 years with influenza, if there is an increased risk of a severe course, there is no additional benefit of baloxavir marboxil compared to oseltamivir in the overall consideration of the results on mortality, morbidity and side effects.

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: In adults and adolescents aged 12 years and above for the treatment of uncomplicated influenza.

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

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

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

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

The G-BA determined symptomatic therapy (antipyretics, antiphlogistics, analgesics) to be the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the double-blind RCT JapicCTI-153090 and CAPSTONE-1.

In both symptomatic therapy with antipyretics and analgesics, with the exception of paracetamol as a "rescue therapy" for severe influenza symptoms, as well as other symptomatic therapies such as antitussives and expectorants or combination cold preparations, were not permitted. Therefore, it is unclear how many subjects would have used symptomatic therapy for symptom relief and how frequently they would take it without the restriction described in the study protocol. Furthermore, no justifications were provided for the extreme differences in the use of paracetamol or for the different maximum daily doses allowed.

For this patient group, no study was presented that would have been suitable for the assessment of the additional benefit of baloxavir marboxil compared with the appropriate comparator therapy. An additional benefit is not proven.

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

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

For this patient group, the pharmaceutical company presents the double-blind RCT CAPSTONE-2, in which baloxavir marboxil was compared with oseltamivir, and the appropriate comparator therapy was thus implemented.

There were no statistically significant differences between the two treatment groups in the categories mortality and side effects. In the category morbidity (influenza symptomatology, health status and influenza-typical complications), there was no statistically significant difference between the treatment groups in subjects with positive influenza detection (presented additionally). Compared to the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the evaluation. There was no assessment of the health-related quality of life.

Uncertainties remain in the additional symptomatic concomitant therapy available, which was severely limited due to the restrictions according to the study protocol.

Overall, for adults and adolescents aged 12 years and above with influenza, if there is an increased risk of a severe course, an additional benefit of baloxavir marboxil compared to oseltamivir 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. 1,091,000 - 1,925,000) and with increased risk of a severe course (approx. 780,000 - 1,378,000) represent 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. 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 company'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 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 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 receives only one antiviral therapy per year or per season; further treatments due to relapses are therefore not included 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				

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Days of treatment/ subject/ year
Baloxavir marboxil	Single dose	1	1	1
Appropriate comparator therapy				
Patient population a)				
symptomatic therapy	patient-individual			
Patient population b)				
Oseltamivir	2 x daily for 5 days	5	1	5
Zanamivir	2 x daily 2 inhalations (equivalent to 2 x daily 2 x 5 mg) for 5 days	5	1	5

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 ≥ 80 kg: 80 mg	40 mg 80 mg	2 x 20 mg 2 x 40 mg	1 1	2 x 20 mg 2 x 40 mg
Appropriate comparator therapy					
Patient population a)					
symptomatic therapy	patient-individual				
Patient population b)					
Oseltamivir	1 x 75 mg	150 mg	2 x 75 mg	5	10 x 75 mg
Zanamivir	1 x 10 mg	20 mg	4 x 5 mg	5	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					
symptomatic therapy	patient-individual				
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 session of the subcommittee 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 20 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