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 Beclometasone/formoterol/glycopyrronium (first dossier requirement: Asthma)

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 combination of active ingredients beclometasone/ formoterol/ glycopyrronium (Trimbow) was approved for the indication COPD on 15 August 2017. The combination of active ingredients was granted new dossier protection with the first marketing authorisation. Trimbow was listed for the first time on 18 August 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 14 January 2021, Trimbow was granted marketing authorisation for a new therapeutic indication under Chapter 5, Section 2, paragraph 2 of the Rules of Procedure (VerfO). The new therapeutic indication bronchial asthma was classified as a major type 2 variation according to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for

human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7). The scope of the benefit assessment resolution according to Section 35a SGB V is opened for Trimbow with the new therapeutic indication bronchial asthma according to Chapter 5, Section 1, Paragraph 2, No. 4a of the Rules of Procedure (VerfO), since the reimbursable medicinal product Trimbow with a new combination of active ingredients, which was first placed on the market on or after 1 January 2011, justified a marketing authorisation for a new therapeutic indication according to Chapter 5, Section 2, Paragraph 2 VerfO and for the first time created an obligation to submit a complete dossier according to Chapter 5, Section 2, paragraph 1, Sentence 3, Number 1, Indent 2 VerfO. In due time on 8 February 2021, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company, on the approval of a new therapeutic indication as amendment of type 2 variation according to Regulation (EC) No. 1234/2008, submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the combination of active ingredients beclometasone/ formoterol/ glycopyrronium (Trimbow) with the new therapeutic indication bronchial asthma.

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 beclometasone/formoterol/glycopyrronium compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by 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 beclometasone/formoterol/glycopyrronium.

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 beclometasone/formoterol/glycopyrronium (Trimbow) according to the product information

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

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 05.08.2021):

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.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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 selection of:

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

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

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. 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. Generally approved for the treatment of asthma are active ingredients of different product classes:

- Beta-2 selective sympathomimetics: Salbutamol, fenoterol, reproterol, salmeterol, formoterol, terbutaline, salbutamol, bambuterol and clenbuterol
- Inhaled anticholinergics: Tiotropium bromide
- Inhaled corticosteroids: Beclometasone, budesonide, ciclesonide, fluticasone and mometasone
- Oral corticosteroids: e.g., prednisolone or prednisone
- Combination preparations: Beclometasone / formoterol, budesonide / formoterol, formoterol / fluticasone, salmeterol / fluticasone, vilanterol / fluticasone, ipratropium bromide / fenoterol, clenbuterol/ ambroxol
- Other: Theophylline, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab

on 2. For the treatment of not adequately controlled asthma, no non-medical measures can be considered as the sole appropriate comparator therapy.

on 3. The following resolutions on an amendment of the Pharmaceuticals Directive (AM-RL) are available:

- Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Indacaterol acetate / glycopyrronium bromide/ mometasone furoate (resolution of 4 February 2021)
- Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dupilumab (resolution of 20 March 2020)
- Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Mepolizumab (resolution of 22 March 2019)
- Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Benralizumab (resolution of 2 August 2018)
- Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Reslizumab (resolution of 6 July 2017)
- Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Mepolizumab (resolution of 21 July 2016)
- Annex IV: Therapeutic information for omalizumab (resolution of 17 December 2015)
- Annex XII / Annex IX: Definition of reference price groups fluticasone furoate/vilanterol

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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 medicinal stage scheme for adults of the National Health Care Guideline Asthma (NVL Asthma 2020, 4th edition, version 1) should be taken into account. The wording of the proposed therapeutic indication does not limit the therapeutic indication to a specific level of the NVL Asthma. However, based on the active ingredient character of the combination beclometasone/ formoterol/ glycopyrronium, the G-BA determines the appropriate comparator therapy for patients who are eligible for therapy according to stage 4 of the NVL Asthma 2020. Accordingly, it is assumed that the patients in the therapeutic indication received at least a two-drug combination (according to NVL Asthma of medium-dose ICS and LABA) as prior therapy and are thus not sufficiently controlled. In addition, it is assumed that patients are not yet eligible for antibody administration.

The guidelines state that the preferred treatment option in stage 4 for adults is a medium- to high-dose ICS in combination with a LABA; alternatively, additional therapy with a long-acting inhaled anticholinergic (LAMA) is recommended. Whether (if asthma is not adequately controlled) an increase in ICS dose or a triple combination with a LAMA is tried first should be decided on a patient-individual basis.

Accordingly, for adults with asthma who are inadequately controlled with medium-dose ICS/LABA therapy, patient-individual therapy escalation is determined, taking into account prior therapy, disease severity, and symptomatology, with a selection of

medium-dose ICS and LABA and LAMA or high-dose ICS and LABA as the appropriate comparator therapy (patient group a). Patient-individual therapy refers to selecting product classes, not to selecting individual active ingredients within the product classes.

According to the guideline, in stage 4 for adults with asthma who are not adequately controlled with high-dose ICS/LABA therapy, additional therapy with a long-acting inhaled anticholinergic (LAMA) is indicated. Accordingly, a therapy consisting of high-dose ICS and LABA and LAMA is determined as the appropriate comparator therapy for this group of patients (patient group b).

The G-BA assumes that the fixed triple combination beclometasone/ formoterol/ glycopyrronium if it contains high-dose ICS, is compared with the appropriate comparator therapy of high-dose ICS and LABA and LAMA (see patient group b).

The unchanged continuation of an inadequate therapy of asthma, if the option of therapy escalation still exists, does not correspond to an appropriate comparator therapy in uncontrolled asthma

Montelukast is only approved as an add-on treatment in patients suffering from mild to moderate persistent asthma. Due to its narrow therapeutic range, theophylline is not the substance of first choice in asthma therapy and is therefore not determined as an appropriate comparator therapy.

The marketing authorisations and product information for the medicinal product of the appropriate comparator therapy must be observed.

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 beclometasone/formoterol/glycopyrronium is assessed as follows:

a) <u>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</u>

An additional benefit is not proven.

Justification:

The pharmaceutical company does not submit any data for the assessment of the additional benefit as they could not identify any suitable studies for a comparison with the appropriate comparator therapy. An assessment of the additional benefit is not possible data basis. Therefore, an additional benefit is not proven.

b) <u>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</u>

An additional benefit is not proven.

Justification:
For the benefit assessment, the pharmaceutical company uses the results of the 3-arm randomised controlled trial TRIGGER, in which the triple combination beclometasone/ formoterol/ glycopyrronium (BDP/Form/Glyc) is compared with beclometasone/ formoterol (BDP/Form) and BDP/Form + tiotropium. Since the administration of tiotropium was in the form of additional inhalations, the study was blinded only for the first two study arms. The study included adult patients up to and including 75 years of age whose asthma was not adequately controlled despite pretreatment with high-dose ICS and LABA. In addition to a score of at least 1.5 on the Asthma Control Questionnaire (ACQ)-7, study participants should have experienced at least 1 asthma exacerbation requiring treatment with systemic corticosteroids, an emergency room visit, or hospitalisation in the year before the start of the study.
The treatment duration was 52 weeks. The primary endpoints of the TRIGGER study are the change in FEV1-value at week 26 and the number of moderate and severe asthma exacerbations over the 52-week treatment period. The study was conducted between April 2016 and May 2018 in Argentina, Belarus, Bulgaria, Czech Republic, Germany, Hungary, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Spain, Turkey, Ukraine and the United Kingdom.

As the appropriate comparator therapy is only implemented in the comparator arm with the triple combination BDP/Form + tiotropium, the comparator arm with the dual combination BDP/Form is not considered for the benefit assessment.

Extent and probability of the additional benefit

Mortality

For the endpoint overall mortality no statistically significant difference was detected between the treatment groups.

Morbidity

Severe asthma exacerbations

Severe asthma exacerbations were defined as the deterioration of asthma symptoms that required treatment with systemic corticosteroids for at least three days. In the resolution, the endpoint is presented as an adjusted annual rate and, in addition, as the number of patients with severe asthma exacerbations.

For the endpoint severe asthma exacerbations no statistically significant difference was detected between the treatment groups.

Asthma symptoms (recorded in a patient diary)

For recording asthma symptoms, evaluations of an electronic patient diary and evaluations of the Asthma Control Questionnaire (ACQ-5) are available. In the patient diary, the patients had to answer in the morning and in the evening whether or with which degree of severity symptoms occurred at night or during the day. The symptoms of coughing, wheezing, chest tightness and respiratory distress/shortness of breath were also explicitly recorded. The ACQ-5 was completed after 4, 12, 26, 40, and 52 weeks of treatment. The questions also cover the symptomatology and refer to the last 7 days. Both instruments are suitable for recording asthma symptoms. For the present benefit assessment, the results of the patient diary are used, as this, in contrast to the ACQ-5, was filled out daily, and the symptomatology was consequently mapped more reliably.

The resolution shows the evaluation of the change from the run-in phase in the percentage of asthma symptom-free days (asthma symptom score = 0 for day and night) over the 52-week study period.

No statistically significant difference was detected between the treatment groups for the endpoint asthma symptoms assessed by the patient diary.

Health status (EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The VAS of the EQ-5D is a visual analogue scale from 0 to 100 on which study participants rate their health status. A value of 0 corresponds to the worst possible health status and a value of 100 to the best possible health status.

There was no statistically significant difference between the treatment groups for the endpoint health status assessed by EQ-5D VAS.

Quality of life

No data on health-related quality of life were assessed.

Side effects

Adverse events (AEs)

During the study period, a comparable number of patients in the intervention arm (71.8%) and the control arm (73.2%) experienced at least one AE (adverse event).

Serious adverse events (SAE)

When recording SAEs, events for the preferred term (PT) "asthma" were also recorded. However, SAEs are relevant for the early benefit assessment without those events that can be attributed to the underlying disease. Although the pharmaceutical company submitted evaluations without events related to severe exacerbations as part of its statements, the analysis still includes events related to PT "asthma", which - like events related to severe exacerbations - are also attributable to the underlying disease. For an adequate evaluation of SAE, an evaluation without any events of the underlying disease would have been necessary, but this was not provided. For this reason, the data on SAEs in the dossier and the data submitted subsequently in the written statement procedure cannot be assessed.

Discontinuation due to AE and major adverse cardiovascular event (MACE)

For the endpoints discontinuation due to AEs and MACE no statistically significant difference was detected between the treatment groups.

Overall assessment / conclusion

For the benefit assessment of beclometasone/ formoterol/ glycopyrronium for 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 past year, results of the randomised controlled study TRIGGER are available for the endpoint categories mortality, morbidity and side effects compared to treatment with beclometasone/ formoterol + tiotropium.

For the endpoint overall mortality no statistically significant difference was detected between the treatment groups.

For the endpoints severe asthma exacerbations, asthma symptomatology and health status (measured by EQ-5D VAS) of the morbidity category, there was also no statistically significant difference between the treatment groups.
Data on health-related quality of life were not collected.

There was no statistically significant difference between the treatment groups for the endpoints discontinuation due to AEs and MACE in the category side effects.
An evaluation of the data on SAEs is not possible, as events related to PT "asthma" were included in the analyses presented. With their statement, the pharmaceutical company has submitted evaluations regarding SAEs without severe asthma exacerbations. However, events related to PT "asthma" are still included in the evaluation. Therefore, the data submitted on the SAEs are still not usable.

Overall, based on the data presented, there is no evidence of an additional benefit of beclometasone/ formoterol/ glycopyrronium compared with treatment with beclometasone/ formoterol + tiotropium for the treatment of 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 past year.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the combination of active ingredients beclometasone/ formoterol/ glycopyrronium, which for the first time imposes an obligation to submit a complete dossier:

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

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

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

About patient group a):

The G-BA determined a patient-individual therapy escalation as an appropriate comparator therapy, taking into account the previous therapy, the severity of the disease and the symptomatology, with a choice of medium-dose ICS and LABA and LAMA or high-dose ICS and LABA.

The pharmaceutical company does not submit any data for the assessment of the additional benefit as they could not identify any suitable studies for a comparison with the appropriate comparator therapy. An additional benefit is not proven.

About patient group b):

A therapy consisting of high-dose ICS and LABA and LAMA was determined by the G-BA as an appropriate comparator therapy.

For the benefit assessment of beclometasone/ formoterol/ glycopyrronium, results of the 3-arm randomised controlled study TRIGGER are available for the endpoint categories mortality, morbidity and side effects compared to treatment with beclometasone/ formoterol + tiotropium. The comparator arm with the two-drug combination beclometasone/ formoterol is not considered for the benefit assessment because the appropriate comparator therapy has not been implemented.

For the endpoint overall mortality no statistically significant difference was detected between the treatment groups.

For the endpoints severe asthma exacerbations, asthma symptomatology and health status (measured by EQ-5D VAS) of the morbidity category, there was also no statistically significant difference between the treatment groups.

Data on health-related quality of life were not collected.

There was no statistically significant difference between the treatment groups for the endpoints discontinuation due to AEs and MACE in the category side effects.
It is not possible to evaluate SAEs because the submitted evaluations contain events related to PT "asthma", which, however, are attributable to the underlying disease.

Based on the data presented in the overall assessment, an additional benefit is not proven for beclometasone/ formoterol/ glycopyrronium compared to treatment with beclometasone/ formoterol + tiotropium.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers provided in the dossier by the pharmaceutical company, which are, however, subject to uncertainties in some areas. When determining the proportion of adults with medium- or high-dose ICS + LABA and the proportion of adults with uncontrolled asthma under therapy with medium- or high-dose ICS + LABA, the proportion values derived by the pharmaceuticals company from the studies considered are partly uncertain or unclear. In addition, the pharmaceutical company does not further restrict the patient population to those patients who have experienced at least 1 asthma exacerbation in the past year.

According to the above-mentioned specifications, no information is available on the division of the target population into the two patient groups.

Overall, the pharmaceutical company's data on the number of patients in the SHI target population are overestimated, taking into account the uncertainties listed.

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 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

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).

In deriving the appropriate comparator therapy costs, the most cost-effective representative was presented for the inhaled synthetic corticosteroids (ICS), long-acting beta-2-adrenergic agonists (LABA), and ICS + LABA fixed combinations.

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. 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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Beclometasone/formoterol/ glycopyrronium	continuously, twice a day	365	1	365
Patient population a)				
Appropriate comparator therapy				
Medium-dose ICS and LABA and LAMA				
Inhaled corticosteroids (ICS, medium dose)				
Ciclesonide	continuously, once a day	365	1	365
long-acting beta-2-adrenergic agonists (LABA)				
Formoterol	continuously, twice a day	365	1	365
ICS/LABA fixed combinations (medium dose)				
Salmeterol/ fluticasone	continuously, twice a day	365	1	365
Long-acting muscarinic receptor antagonists (LAMA)				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Tiotropium	continuously, once a day	365	1	365
OR				
High-dose ICS and LABA				
Inhaled synthetic corticosteroids (ICS, high dose)				
Budesonide	continuously, twice a day	365	1	365
Long-acting beta-2-adrenergic agonists (LABA)				
Formoterol	continuously, twice a day	365	1	365
ICS/LABA fixed combinations (high dose)				
Salmeterol/ fluticasone	continuously, twice a day	365	1	365
Patient population b)				
Appropriate comparator therapy				
High-dose ICS and LABA and LAMA				
Inhaled synthetic corticosteroids (ICS, high dose)				
Budesonide	continuously, twice a day	365	1	365
Long-acting beta-2-adrenergic agonists (LABA)				
Formoterol	continuously, twice a day	365	1	365
ICS/LABA fixed combinations (high dose)				
Salmeterol/ fluticasone	continuously, twice a day	365	1	365
Long-acting muscarinic receptor antagonists (LAMA)				
Tiotropium	continuously, once a day	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
ICS/LABA/ LAMA fixed combinations (high dose)				
Indacaterol/ glycopyrronium/ mometasone	continuously, once a day	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Beclometasone/ formoterol/ glycopyrronium 87 µg/5 µg/9 µg	100/6/10 µg	400/24/ 40 µg	4 x 100/6/10 µg	365	1460 x 100/6/10 µg
Beclometasone/ formoterol/ glycopyrronium 172 µg/5 µg/9 µg	200/6/10 µg[2]	800/24/ 40 µg	4 x 200/6/10 µg	365	1460 x 200/6/10 µg
Appropriate comparator therapy					
Patient population a)					
Medium-dose ICS and LABA and LAMA					
Inhaled corticosteroids (ICS, medium dose)					
Ciclesonide	160 µg	160 µg	1 x 160 µg	365	365 x 160 µg
long-acting beta-2-adrenergic agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	730	730 x 12 µg
ICS/LABA fixed combinations (medium dose)					

[2] Currently not available

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Salmeterol/ fluticasone	125 µg/ 25 µg - 250 µg/ 50 µg	250 µg/ 50 µg - 500 µg/ 100 µg	2 x 125 µg/25 µg – 2 x 250 µg/ 50 µg	365	730 x 125 µg /25 µg – 730 x 250 µg/ 50 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
OR					
High-dose ICS and LABA					
Inhaled synthetic corticosteroids (ICS, high dose)					
Budesonide	400 µg	800 µg	2 x 400 µg	365	730 x 400 µg
long-acting beta-2-adrenergic agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	730	730 x 12 µg
ICS/LABA fixed combinations (high dose)					
Salmeterol/ fluticasone	500 µg /50 µg	1,000 µg/ 100 µg	2 x 500 µg /50 µg	365	730 x 500 µg /50 µg
Patient population b)					
High-dose ICS and LABA and LAMA					
Inhaled synthetic corticosteroids (ICS, high dose)					
Budesonide	400 µg	800 µg	2 x 400 µg	365	730 x 400 µg
long-acting beta-2-adrenergic agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	730	730 x 12 µg
ICS/LABA fixed combinations (high dose)					
Salmeterol/ fluticasone	500 µg /50 µg	1,000 µg/ 100 µg	2 x 500 µg /50 µg	365	730 x 500 µg /50 µg
Long acting muscarinic receptor antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
ICS/LABA/ LAMA fixed combinations (high dose)					
Indacaterol/ glycopyrronium/ mometasone	114 µg/ 46 µg/ 136 µg	114 µg/ 46 µg/ 136 µg	1 x 114 µg/ 46 µg/136 µg	365	365 x 114 µg/

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
					46 µg/ 136 µg

Costs:

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					
Beclometasone/ formoterol/ glycopyrronium 87 µg/5 µg/9 µg	3 MDI	€ 268.25	€ 1.77	€ 14.24	€ 252.24
Beclometasone/ formoterol/ glycopyrronium 172 µg/5 µg/9 µg	Costs not comprehensible, package price not to be found in LAUER-TAXE®				
Appropriate comparator therapy					
Budesonide 400 µg[3]	3 IHP	€ 63.59	€ 1.77	€ 4.16	€ 57.66
Ciclesonide 160 µg[3]	1 MDI	€ 33.21	€ 1.77	€ 0.00	€ 31.44
Formoterol 12 µg[3]	3 MDI	€ 83.73	€ 1.77	€ 5.75	€ 76.21
Indacaterol/ glycopyrronium/ mometasone 114µg/ 46µg/ 136µg	90 HPI	€ 296.66	€ 1.77	€ 15.81	€ 279.08
Salmeterol/ fluticasone 125 µg/ 25 µg[3]	1 MDI	€ 44.11	€ 1.77	€ 2.62	€ 39.72
Salmeterol/ fluticasone 250 µg/ 50 µg[3]	3 IHP	€ 100.03	€ 1.77	€ 7.04	€ 91.22
Salmeterol/ fluticasone 500 µg/ 50 µg[3]	3 IHP	€ 133.65	€ 1.77	€ 9.70	€ 122.18
Tiotropium 2,5 µg	3 INS	€ 197.59	€ 1.77	€ 10.33	€ 185.49
Abbreviations: MDI = metered dose inhaler, HPI = hard capsules with powder for inhalation, IHP = inhalation powder, INS = inhalation solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there

[3] Fixed reimbursement rate

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 25 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 8 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of beclometasone/formoterol/glycopyrronium to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 3a VerfO.

By letter dated 11 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 beclometasone/formoterol/glycopyrronium.

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 22 June 2021.

By letter dated 22 June 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by IQWiG was submitted to the G-BA on 15 July 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	25 August 2020	Determination of the appropriate comparator therapy
Working group Section 35a	15 June 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 June 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30.06.2021; 13.07.2021; 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