Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Fluticasone furoate/Umeclidinium/Vilanterol (new therapeutic indication: COPD that is not adequately treated by a combination of LAMA and LABA)

of 2 May 2019

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 benefit,
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. Treatment costs for statutory health insurance funds,
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 shall pass a resolution 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 active ingredient combination fluticasone furoate/umeclidinium/vilanterol was listed for the first time on 1 March 2018 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 31 October 2018, fluticasone furoate/umeclidinium/vilanterol received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 number 2 letter to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 15 November 2018, the pharmaceutical company has 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 the active ingredient combination fluticasone furoate/umeclidinium/vilanterol with the new therapeutic indication (COPD not adequately treated with a combination of LAMA and LABA)

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 15 February 2019, 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 fluticasone furoate/umeclidinium/vilanterol 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, 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 fluticasone furoate/umeclidinium/vilanterol.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at 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 fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta® / Elebrato Ellipta®) in accordance with product information

Trelegy Ellipta/Elebrato Ellipta is indicated as a 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 corticosteroid and a long-acting β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom control and prevention of exacerbations see Section 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA)

Appropriate comparator therapy:

- LABA and LAMA and ICS

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 according to 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 as a comparator therapy, this must be available within the framework of the SHI system.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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. Active ingredients of different classes approved for the treatment of patients with COPD:

- Selective beta-2 sympathomimetics: Formoterol, indacaterol, salbutamol, salmeterol, olodaterol, vilanterol, phenoterol, bambuterol, clenbuterol, terbutamol, reproterol
- Anticholinergics: Aclidinium, glycopyrronium, ipratropium, tiotropium, umeclidinium
- Corticosteroids: Beclometasone, budesonide, fluticasone, methylprednisolone, prednisolone, prednisone, triamcinolone
- Xanthines: Aminophylline, theophylline
- Phosphodiesterase inhibitors: Roflumilast

Various combinations of long-acting selective beta-2 sympathomimetics (LABA), long-acting anticholinergics (LAMA), and inhaled corticosteroids (ICS) are available. In addition, some of the individual active ingredients listed are not available in a monopreparation but rather only in a fixed combination product.

The marketing authorisations of the medicinal products must be observed.

On 2. Non-medicinal treatment is not an appropriate comparator therapy for the present therapeutic indication.

On 3. The following resolutions have been passes by the G-BA on an amendment to the AM-RL: Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V:

- Indacaterol/glycopyrronium: Resolution of 8 May 2014 (for patients in Stage II: Hint for a minor additional benefit; for Stage III patients with one exacerbation per year: Indication for a minor additional benefit; for all other patients: additional benefit is not proven)
- Olodaterol: Resolution of 17 July 2014 (additional benefit considered not to be proven, reference amount group formation “Beta2 sympathomimetics, inhaled orally”, Group 1, in Stage 2)
- Umeclidinium/vilanterol: Resolution of 8 January 2015 (no proof of additional benefit compared with appropriate comparator therapy)
- Aclidinium bromide/formoterol – Resolution of 16 July 2015 (for Stage II patients: Indication for a minor additional benefit; for Stage III patients with one exacerbation per year: Indication for a considerable additional benefit; for all other patients: additional benefit is not proven)
- Tiotropium/olodaterol: Resolution of 4 February 2016 (for patients with a moderate degree of severity or more: Indication of a minor additional benefit; for patients with a higher degree of severity and ≥ 2 exacerbations per year: Hint for a minor benefit
- Aclidinium bromide: Resolution of 7 April 2016 (for patients in Stage II: An additional benefit is not proven; for Stage III patients with < 2 exacerbations per year: Indication for a considerable additional benefit; for all other patients: additional benefit is not proven)
- Umeclidinium: Resolution of 21 July 2016 (additional benefit is not proven)
- Fluticasone furoate/umeclidinium/vilanterol: Resolution of 16 August 2018 (additional benefit is not proven)

On 4. The general state of medical knowledge on which the finding of the G-BA is based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

The therapeutic indication of the triple combination fluticasone furoate/umeclidinium/vilanterol to be evaluated includes the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated with a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA). It is therefore assumed that the patients for whom the active ingredient combination is suitable continue to exhibit symptoms (including exacerbations).

In patients who continue to experience exacerbations despite existing treatment with LABA and LAMA, the current recommendations give priority to adjunctive therapy with inhaled cortocosteroids (ICS). The change from an existing therapy with LABA and LAMA to a therapy with LABA and ICS is still recommended as an alternative by individual guidelines. However, it does not represent an equivalent therapy option based on the latest findings and guideline recommendations. The current GOLD Guideline (2019) states that escalation with ICS in addition to LABA and LAMA is recommended, especially for patients who continue to have exacerbations despite existing therapy with LABA and LAMA. Exacerbations under therapy with LABA and LAMA in COPD patients indicate an additional inflammatory component of COPD for which corticosteroids are usually indicated. The phosphodiesterase inhibitor roflumilast is approved for the treatment of patients with severe COPD (FEV1 < 50%) and chronic bronchitis and a history of frequent exacerbations. It can therefore be considered in patients who show further symptoms (e.g. frequent exacerbations) as part of therapy optimisation. Roflumilast is therefore only suitable for a very limited group of patients with chronic bronchitis symptomology. For the vast majority of patients with moderate to severe COPD who continue to have exacerbations when treated with a dual therapy of LABA and LAMA, adjunctive therapy with ICS represents the appropriate comparator therapy according to the current state of scientific knowledge.

Short-acting bronchodilators should normally only be used when required and can be used as an adjuvant medication with any severity of COPD. Xanthines (e.g. theophylline) have a relatively small therapeutic range and do not regularly form part of the appropriate comparator therapy for the treatment of COPD.

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

<u>Adjustment of the appropriate comparator therapy:</u>

For adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), a “patient-individual therapy optimisation of the existing LABA + LAMA therapy with LABA + LAMA and possibly ICS” was originally determined as an appropriate comparator therapy. This resolution amends this appropriate comparator therapy as follows, taking into account the opinions of medical societies and experts in the present procedure as well as the generally recognised state of medical knowledge:
The appropriate comparator therapy for adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is a combination therapy of LABA and LAMA and ICS.

Also in the originally determined appropriate comparator therapy, escalation with ICS was already named as an option within the scope of patient-individual therapy optimisation in addition to the existing therapy of LABA and LAMA. At that time, there was not sufficient evidence that escalation to triple therapy with ICS was preferable to double therapy. Thus, both options were reflected in the guidelines. However, the results of recent studies have

shown that patients who are not adequately controlled with a dual combination of LABA and LAMA have a lower annual rate of moderate or severe exacerbations with a triple combination of LABA and LAMA and ICS compared with a dual combination of LABA and LAMA or LABA and ICS. One of these studies is the randomized, controlled, double-blind IMPACT study submitted for the present benefit assessment. This examines the fixed triple combination fluticasone furoate/umeclidinium/vilanterol (ICS and LAMA and LABA) in comparison with the fixed dual combinations fluticasone furoate/vilanterol or umeclidinium/vilanterol.

It can be assumed that the results of the studies had a relevant influence on the adaptation of the current recommendations of the 2019 GOLD Guideline: For patients with COPD who are not adequately treated with a combination of LABA and LAMA (i.e. who continue to suffer from exacerbations), only an escalation to a triple therapy is recommended. For the vast majority of these patients, only additional therapy with ICS can be considered. This recommendation on the current therapy standard was unanimously confirmed in the written and oral statements on the current benefit assessment procedure.

An adjustment of the appropriate comparator therapy is justified and necessary because of the influence of the studies for the fixed triple combination to be considered here on the current state of medical knowledge. In addition, representatives of the three active ingredient classes LABA, LAMA and ICS have been available for some time as combination therapy or as individual substances for the therapeutic indication COPD. In Germany, they are already used to a significant extent in the triple combination[2]. Within a class, currently no active ingredient is to be used as a priority. All active ingredients of a class are therefore equally regarded as appropriate therapy options.

At the present time, the patient-individual assessment between dual- and triple therapy is no longer a useful comparison for patients with moderate to severe COPD who are not adequately treated with a combination of LABA and LAMA.

2.3.1. Extent and probability of the additional benefit

In summary, the additional benefit of fluticasone furoate/umeclidinium/vilanterol is assessed as follows:

Adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA):

An additional benefit is not proven.

Justification:

In order to demonstrate the additional benefit for the benefit assessment of fluticasone furoate/umeclidinium/vilanterol, the pharmaceutical company has submitted the results of the sub-populations of the IMPACT and FULFIL studies that conform to the regulatory requirements.

IMPACT study

The randomised, controlled, double-blind IMPACT study was conducted between June 2014 and July 2017. It investigated the once-daily inhalation of the fixed triple combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in comparison with the fixed dual combination fluticasone furoate/vilanterol (FF/VI) and the fixed dual combination umeclidinium/vilanterol (UMEC/VI) in patients with COPD. Inclusion criteria included patients 40 years of age and older with confirmed and symptomatic COPD who had a smoker history of at least 10 pack years. For these patients at least one moderate or severe exacerbation had to be documented within the last 12 months before screening. The patients included

[2] Graf J, Jörres et al. (2018): Medical treatment of COPD—an analysis of guideline-adherent prescribing in a large national cohort (COSYCONET). Dtsch Arztebl Int 2018; 115: 599–605. DOI: 10.3238/arztebl.2018.0599

showed moderate to very severe respiratory obstruction (degrees of severity of 2 to 4 according to GOLD[3]) despite COPD maintenance treatment of at least three months prior to inclusion.

The IMPACT study included a two-week run-in phase in which COPD maintenance treatment was maintained, a randomised treatment phase of 52 weeks, and a follow-up phase of seven days. A total of 10,367 patients were randomised to the three arms (2:2:1): 4,155 patients in the FF/UMEC/VI arm, 4,139 patients in the FF/VI arm, and 2,073 patients in the UMEC/VI arm. In the course of the study, short-term treatment (≤ 14 days) of exacerbations or pneumonia with systemic corticosteroids, antibiotics or, at the doctor's discretion, other COPD medications was possible. The use of salbutamol as rescue medication was also permitted.

According to the therapeutic indication of FF/UMEC/VI, only the results of the sub-population of the IMPACT study for which maintenance treatment prior to inclusion consisted of at least one LAMA and one LABA (LAMA + LABA) and contained no ICS were presented in the dossier (approx. 9% of patients received a xanthine and/or a phosphodiesterase-4 inhibitor in addition to LAMA and LABA). This sub-population of the IMPACT study, referred to by the pharmaceutical company as the "ITT-LAMA+LABA population", comprises 389 patients in the FF/UMEC/VI arm, 349 patients in the FF/VI arm, and 196 patients in the UMEC/VI arm.

FULFIL study

The randomised, double-blind, controlled FULFIL study was conducted between January 2015 and April 2016. It investigated the administration of the fixed triple combination FF/UMEC/VI versus the dual combination of budesonide and formoterol in patients with COPD.

The study included patients 40 years of age and older with confirmed and symptomatic COPD who had a smoker history of at least 10 pack years. For these patients, at least two moderate or one severe exacerbation must have been documented within the last 12 months prior to screening provided that the post-bronchodilator FEV1% set-point was ≥ 50 and < 80%. Otherwise, the post-bronchodilator FEV1% set-point must be < 50%. The patients included showed moderate to very severe respiratory obstruction (degrees of severity of 2 to 4 according to GOLD[4]) despite COPD maintenance treatment of at least three months prior to inclusion.

The FULFIL study included a two-week run-in phase in which COPD maintenance treatment was maintained before study inclusion, a randomised treatment phase of 52 weeks, and a follow-up phase of seven days. A total of 1811 patients were randomized to the FF/UMEC/VI arm (911 patients) or the BUD/FOR arm (900 patients). In the course of the study, short-term treatment (≤ 14 days) of exacerbations or pneumonia with systemic corticosteroids, antibiotics or, at the doctor's discretion, other COPD medications was possible. The use of salbutamol as rescue medication was also permitted.

Analogous to the procedure in the IMPACT study, the pharmaceutical company submitted only the data of the patients in the FULFIL study who received maintenance treatment with LAMA and LABA prior to inclusion in the study and whose maintenance treatment did not include ICS for the present therapeutic indication of FF/UMEC/VI in the dossier. This sub-population of the FULFIL study comprises 114 patients in the intervention arm and 98 patients in the control arm ("ITT-LAMA + LABA population").

Implementation of the appropriate comparator therapy in the IMPACT and FULFIL studies

In both studies, the patients included showed moderate to very severe respiratory obstruction (degrees of severity of 2 to 4 according to GOLD) despite COPD maintenance treatment of at least three months prior to inclusion. In both studies, the patient populations were

[3] GOLD = Global Initiative for Chronic Obstructive Lung Disease (GOLD).
[4] GOLD = Global Initiative for Chronic Obstructive Lung Disease (GOLD).

approximately comparable: patients in the relevant sub-populations showed an average CAT score[5] of about 18 to 20 for study inclusion, indicating a pronounced burden of symptoms. In addition, 66% of the patients in the IMPACT study and 54% and 51% of the patients in the FULFIL study (in the intervention arm and control arm, respectively) experienced ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation in the year prior to inclusion in the study.

In the IMPACT study, the therapy for all patients in the intervention arm was escalated from the dual combination LABA/LAMA to the triple combination consisting of LABA and LAMA and ICS (FF/UMEC/VI), whereas the patients in the control arm were either switched to a dual therapy of ICS and LABA (fluticasone furoate/vilanterol) or maintained on a therapy with a combination of LABA and LAMA (umeclidinium/vilanterol).
Also in the FULFIL study, all patients in the intervention arm were escalated to the triple combination consisting of LABA and LAMA and ICS (FF/UMEC/VI), whereas the patients in the control arm were switched to a dual therapy consisting of ICS and LABA (budesonide/formoterol).

However, for patients who have further exacerbations under a dual therapy of LABA and LAMA, escalation to a triple combination of LABA and LAMA and ICS would be indicated based on the current therapy recommendations. According to the appropriate comparator therapy adapted to the current state of medical knowledge, it would have been necessary for all patients in the comparator arms to escalate with ICS in addition to their existing therapy of LABA and LAMA.

Also in the originally determined appropriate comparator therapy, escalation with ICS was already named as an option within the scope of patient-individual therapy optimisation in addition to the existing therapy of LABA and LAMA. From the point of view of the G-BA, it would also have been necessary at this point in time to offer at least all patients in the studies the additional administration of ICS in the comparator arm (at the start of study and possibly during the course of the study). Instead, the patients in the ICS/LABA comparator arm of the studies switched to the dual combination of ICS and LABA despite persistent symptomology with a dual combination of LABA and LAMA, and therapy with LAMA was not continued. Furthermore, it is unclear how large the proportion of patients is who had already received previous therapy with ICS prior to dual therapy with LABA and LAMA and for whom therapy with ICS and LABA might no longer have been indicated.

Taken together, in both studies an additional escalation with ICS was not possible according to the specifications of the appropriate comparator therapy determined by the G-BA. It can thus be assumed that the patients in the comparator arm were not treated according to the current state of medical knowledge. Because the appropriate comparator therapy determined by the G-BA was not implemented in the IMPACT and FULFIL studies, these cannot be used to derive the additional benefit of FF/UMEC/VI.

Even if the studies do not provide any data compared with the currently determined appropriate comparator therapy, because of their clinical significance, the results of the IMPACT and FULFIL studies will be presented and discussed in the following. According to the clinical experts, the significance of the studies lies particularly in the fact that the results for COPD patients who are not adequately treated with LABA and LAMA show that triple therapy with ICS and LABA and LAMA is preferable to dual therapy with ICS and LABA.

In the following, the results of the relevant sub-population[6,7] of the IMPACT and FULFIL studies are presented in addition. These show a comparison of triple therapy with a dual therapy of ICS and LABA[8]:

Mortality

In the IMPACT study, deaths were recorded via the endpoint “total mortality” and the survey of adverse events (SAE with fatal outcome).

[5] CAT = COPD Assessment Test.
[6] ITT-LAMA + LABA population: Sub-population of patients from the IMPACT and FULFIL studies receiving pretreatment with LABA and LAMA.
[7] Unless otherwise indicated, data from the addendum of the IQWiG (A19-27 of 12 April 2019).
[8] In the respective control arm all patients received therapy with ICS and LABA (fluticasone furoate and vilanterol in the IMPACT study and budesonide and formoterol in the FULFIL study).

In terms of overall mortality (deaths occurring during treatment with study medication (between initiation of study treatment and end of follow-up phase (7 days after last administration of study medication))), 6 deaths (1.5%) occurred in the FF/UMEC/VI arm and 2 deaths (0.6%) in the FF/VI arm. The result is not statistically significant between treatment groups. After therapy discontinuation, deaths were recorded further. However, data on the relevant sub-population were not available in the dossier.
Serious adverse events (SAE) with fatal outcome were recorded during treatment with study medication if the onset of the event occurred between the start and end of study treatment + 1 day. In this operationalisation, the outcome of an SAE (and correspondingly also deaths) that occurred after the follow-up phase and thus more than seven days after the last administration of the study medication was taken into account. Patients who discontinued the study medication early are recorded only up to this point. After therapy discontinuation, SAE with a fatal outcome continued to be recorded. However, data on the relevant sub-population are not available. There were seven deaths (1.8%) in the FF/UMEC/VI arm and five deaths (1.4%) in the FF/VI arm. The result is not statistically significant between treatment groups.

In the FULFIL study, deaths were recorded via the survey of adverse events. One death occurred in the study. There was no statistically significant difference between the treatment groups.

Morbidity

Exacerbations

For the endpoint exacerbations of the two studies, the results of the "Annual exacerbation rate" ("moderate or severe exacerbations" or "severe exacerbations") and the "Proportion of patients with event" were available.

In the IMPACT study, the endpoint "Moderate or severe exacerbations", the annual exacerbation rate was 0.84 in the FF/UMEC/VI arm and 1.11 in the FF/VI arm (47% and 48% of patients had exacerbations within 52 weeks). For the endpoint "severe exacerbations", the annual exacerbation rate was 0.14 in the FF/UMEC/VI arm and 0.13 in the FF/VI arm (11% and 9% of patients had exacerbations within 52 weeks). The rate ratio of the annual exacerbation rates for "moderate or severe exacerbations" is thus 0.76 (95% CI [0.62; 0.94], $p < 0.001$) and is therefore statistically significant in favour of FF/UMEC/VI. For "severe exacerbations" the rate ratio is 1.04; the result is not statistically significant between treatment groups.

In the FULFIL study, the annual exacerbation rate for the endpoint "Moderate or severe exacerbations" was 0.38 in the FF/UMEC/VI arm and 0.27 in the control arm (18% and 14% of patients had exacerbations within 24 weeks, respectively). In each of the two study arms, severe exacerbations occurred in two patients. For both endpoints, there was no statistically significant difference between the treatment groups.

CAT responders
The COPD Assessment Test (CAT) assesses the COPD symptomology and the associated impairments in the patient's everyday life. For the endpoint "CAT responder" (reduction of the CAT score by ≥ 2 points), no statistically significant difference between the treatment groups was found in both studies.

Patient Global Rating (PGR) and European Quality of Life Questionnaire 5 Dimensions (visual analogue scale, EQ-5D VAS)
In the two studies, the health status of the patients was assessed using PGR and EQ-5D VAS. In the IMPACT study, there was no statistically significant difference between the treatment arms in both questionnaires.
In the FULFIL study, no usable data are available for the EQ-5D VAS. With regard to PGR, a higher proportion of patients in the FF/UMEC/VI arm reported improved severity of COPD after 24 weeks of treatment ("much better", "better", or "slightly better"), wherein the patients

in the control arm classify the severity of COPD mainly as unchanged or worsened (OR = 0.42 95% CI [0.24; 0.72]; p = 0.002).

Quality of life

SGRQ responders
The health-related quality of life was assessed using the *St. George's Respiratory Questionnaire* (SGRQ). Patients with a reduction of the total score by at least 4 scale points were evaluated as responders, whereby a reduction of the score means an improvement.

The IMPACT study showed a statistically significant advantage in quality of life in favour of FF/UMEC/VI versus FF/VI as measured by the SGRQ responders at week 52 (37% vs 29%; RR = 1.27; 95% CI [1.03; 1.57]; p = 0.024).

In the FULFIL study, there was no statistically significant difference in quality of life between the treatment arms at week 24.

Side effects

Adverse events (AE) and discontinuation because of AE
For SAE (non-fatal, no exacerbation events) and AE that led to therapy discontinuation (no exacerbation events), the IMPACT study and the FULFIL showed no statistically significant difference between treatment groups at week 52 and week 24, respectively.

Specific AE
Cardiovascular events
For the cardiovascular events endpoint, there was no usable data from the IMPACT and 200812 studies.

Pneumonia
In the two studies, there were no statistically significant differences between the treatment groups with regard to pneumonia.

Conclusions of the IMPACT and FULFIL studies

In both studies, the patients included showed moderate to very severe respiratory obstruction (degrees of severity of 2 to 4 according to GOLD) despite COPD maintenance treatment of at least three months prior to inclusion. In the IMPACT study, the therapy for all patients in the intervention arm was escalated from the dual combination LABA and LAMA to the triple combination consisting of LABA and LAMA and ICS (FF/UMEC/VI), whereas the patients in the control arm were either switched to a dual therapy of ICS and LABA (fluticasone furoate/vilanterol) or maintained on a therapy with a combination of LABA and LAMA (umeclidinium/vilanterol).
Also in the FULFIL study, all patients in the intervention arm were escalated to the triple combination FF/UMEC/VI, whereas patients in the control arm were switched to a dual therapy of ICS and LABA (budesonide/formoterol).

However, for patients who have further exacerbations under a dual therapy of LABA and LAMA, escalation to a triple combination of LABA and LAMA and ICS would be indicated based on the current therapy recommendations. According to the appropriate comparator therapy adapted to the current state of medical knowledge, it would have been necessary for all patients in the comparator arms to escalate with ICS in addition to their existing therapy of LABA and LAMA. Instead, therapy with LAMA was not continued in the ICS/LABA comparator arm despite persistent symptomology, and all patients switched to the dual combination of ICS and LABA. In addition, in both studies no therapy adjustment was possible during the course of the study. Taken together, in both studies, the appropriate comparator therapy was not implemented. It can be assumed that the patients in the comparator arm were not treated according to the current state of medical knowledge. Against this background, both studies cannot be used to derive the additional benefit of FF/UMEC/VI.

However, the results of the relevant sub-population of the IMPACT study show a statistically significant advantage of the administration of FF/UMEC/VI compared with FF/VI in terms of the annual rate of moderate and severe exacerbations as well as in terms of quality of life (measured by the SGRQ responder). The FULFIL study shows advantages of FF/UMEC/VI over BUD/FOR in terms of severity of COPD (measured by PGR) for the corresponding sub-population. For all other endpoints of morbidity, mortality and side effects, there were no statistically significant differences between the treatment groups in both studies.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI). The therapeutic indication of FF/UMEC/VI relevant for the benefit assessment is as follows: “Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA)”. The G-BA determined “LABA and LAMA and ICS” as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company provided data from the corresponding sub-populations of the IMPACT and FULFIL studies. In both studies, the patients included showed moderate to very severe respiratory obstruction (degrees of severity of 2 to 4 according to GOLD) despite a maintenance treatment of LABA and LAMA of at least three months prior to inclusion. In the IMPACT study, the therapy for all patients in the intervention arm was escalated from the dual combination LABA/LAMA to the triple combination consisting of LABA and LAMA and ICS (FF/UMEC/VI), whereas the patients in the control arm were either switched to a dual therapy of ICS and LABA (FFVI) or maintained on a therapy with a combination of LABA and LAMA (UMECVI).

However, for patients who have further exacerbations under a dual therapy of LABA and LAMA, escalation to a triple combination of LABA and LAMA and ICS would be indicated based on the current therapy recommendations. It can be assumed that the patients in the comparator arm did not receive adequate treatment according to the current state of medical knowledge. For this reason, no statements can be made regarding the additional benefit of FF/UMEC/VI from the IMPACT and FULFIL studies. An additional benefit is thus not proven.

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

This information on the number of patients concerns the target population in the statutory health insurance.
The G-BA bases the resolution on the estimate of the number of patients derived by the pharmaceutical company in the dossier. In estimating the target population, no patients in the age group < 40 years were considered. However, the number of patients stated by the pharmaceutical company in the dossier is subject to uncertainties: The prevalence of COPD in the age group ≥ 40 years from a COPD severity of 2 was derived exclusively from a small and regional study (683 volunteers from the Hanover area) from 2005.
The pharmaceutical company determined the upper and lower limits of the proportion of patients with COPD symptoms on the basis of two sources. However, the upper limit is derived from only a small sample (29 subjects). It cannot be excluded that patients with a lower degree of severity are also included in this sample. In addition, the pharmaceutical company did not use the number and severity of annual exacerbations or a validated questionnaire for derivation.
To calculate the proportion of symptomatic COPD patients from a severity of 2 who are treated with LAMA and LABA, the pharmaceutical company uses the data from the publication on the German COPD register DACCORD and the cohort study COSYCONET.

Because no restriction to symptomatic COPD patients is made in the data, the lower limit determined from the DACCORD register refers to a false population. Furthermore, it cannot be excluded that patients with a lower degree of severity are also included in both samples.

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 Trelegy Ellipta®/Elebrato Ellipta® (active ingredient: fluticasone furoate/umeclidinium/vilanterol) at the following publicly accessible link (last access: 26 March 2019):

https://www.ema.europa.eu/documents/product-information/trelegy-ellipta-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 April 2019).

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

With regard to consumption, the average annual consumption was determined by indicating the number of single doses (ED, equivalent to inhalations). The daily doses recommended in the product information were used as the calculation basis and, if required, corresponding margins were formed.

According to the product information, the fixed combination fluticasone furoate/umeclidinium/vilanterol is used once a day.

When deriving the costs for the appropriate comparator therapy, the active ingredient classes long-acting beta-2 sympathomimetics (LABA), long-acting anticholinergics (LAMA), and inhaled corticosteroids (ICS) were first presented separately and then, if available, as fixed combinations.

The LAMA tiotropium is available as hard capsules with powder for inhalation (Braltus® or Spiriva®, 10 µg tiotropium per capsule) as well as a solution for inhalation (Spiriva® Respimat®, 2.5 µg tiotropium per inhalation). The cost calculation is based on the most cost-effective variant (Braltus®).

The treatment duration, consumption, and costs of treatment with inhaled corticosteroids are shown as examples for beclomethasone and fluticasone. According to the product information, beclomethasone is administered twice daily (1–2 puffs of 200 µg each) and fluticasone twice daily (2 puffs of 250 µg each).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments /patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Fluticasone furoate/umeclidinium/vilanterol	continuous, 1 x daily 1 single dose	365	1	365
Appropriate comparator therapy: - LABA and LAMA and ICS				

Designation of the therapy	Treatment mode	Number of treatments /patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
long-acting beta-2 sympathomimetics (LABA)				
Salmeterol	continuous, 2 x daily 2 single dose	365	1	365
Formoterol	continuous, 2 x daily 1 single dose	365	1	365
Olodaterol	continuous, 1 x daily 2 single doses	365	1	365
Indacaterol	continuous, 1 x daily 1 single dose	365	1	365
long-acting anticholinergics (LAMA)				
Tiotropium[9] (hard capsule)	continuous, 1 x daily 1 single dose	365	1	365
Aclidinium	continuous, 2 x daily 1 single dose	365	1	365
Glycopyrronium	continuous, 1 x daily 1 single dose	365	1	365
Umeclidinium	continuous, 1 x daily 1 single dose	365	1	365
Inhaled corticosteroids (ICS)				
Beclometasone	continuous, 2 x daily 1–2 single doses	365	1	365
Fluticasone	continuous, 2 x daily 2 single dose	365	1	365
Fixed combinations				
- of ICS and LABA				
Beclometasone/formoterol	continuous, 2 x daily 2 single dose	365	1	365
Budesonide/formoterol	continuous, 2 x daily 1 single dose	365	1	365

[9] Tiotropium as hard capsules with powder for inhalation: According to the product information of Braltus®, each hard capsule contains 16 µg tiotropium bromide, which corresponds to 13 µg tiotropium. The amount released from the mouthpiece of the Zonda® inhaler is 10 µg tiotropium per capsule.

Designation of the therapy	Treatment mode	Number of treatments /patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Fluticasone/salmeterol	continuous, 2 x daily 1 single dose	365	1	365
Fluticasone/vilanterol	continuous, 1 x daily 1 single dose	365	1	365
- of LAMA and LABA				
Tiotropium/olodaterol	continuous, 1 x daily 2 single doses	365	1	365
Indacaterol/glycopyrronium	continuous, 1 x daily 1 single dose	365	1	365
Umeclidinium/vilanterol	continuous, 1 x daily 1 single dose	365	1	365
Aclidinium/formoterol	continuous, 2 x daily 1 single dose	365	1	365
- of ICS and LABA and LAMA				
Beclometasone/formoterol/glycopyrronium	continuous, 2 x daily 2 single dose	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Fluticasone furoate/umeclidinium/vilanterol	100 µg/62.5 µg/25 µg	100 µg/62.5 µg/25 µg	1 × 100 µg/62.5 µg/25 µg	365	365 × 100 µg/62.5 µg/25 µg
Appropriate comparator therapy: - LABA and LAMA and ICS					
long-acting beta-2 sympathomimetics (LABA)					
Salmeterol	50 µg	100 µg	2 × 50 µg	365	730 × 50 µg
Formoterol	12 µg	24 µg	2 × 12 µg	365	730 × 12 µg
Olodaterol	5 µg	5 µg	2 × 2.5 µg	365	730 × 2.5 µg
Indacaterol	150 µg or	150 µg or	1 × 150 µg or	365	365 × 150 µg or
	300 µg	300 µg	1 × 300 µg	365	365 × 300 µg

Designation of the therapy	Dosage/application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
long-acting anticholinergics (LAMA)					
Tiotropium[9] (hard capsule)	13 µg	13 µg	1 × 13 µg	365	365 × 13 µg
Aclidinium	343 µg	686 µg	2 × 343 µg	365	730 × 343 µg
Glycopyrronium	50 µg	50 µg	1 × 50 µg	365	365 × 50 µg
Umeclidinium	62.5 µg	62.5 µg	1 × 62.5 µg	365	365 × 62.5 µg
Inhaled corticosteroids (ICS)					
Beclometasone	200 µg	400 µg	2 × 200 µg	365	730 × 200 µg
Fluticasone	500 µg	1000 µg	4 × 250 µg	365	1460 × 250 µg
Fixed combinations					
- of ICS and LABA					
Beclometasone/formoterol	200 µg/ 12 µg	400 µg/ 24 µg	4 × 100 µg/ 6 µg	365	1460 x 100 µg/ 6 µg
Budesonide/formoterol	320 µg/ 9 µg	640 µg/ 18 µg	2 × 320 µg/ 9 µg	365	730 × 320 µg/ 9 µg
Fluticasone/salmeterol	500 µg/ 50 µg	1000 µg/ 100 µg	2 × 500 µg/ 50 µg	365	730 × 500 µg/ 50 µg
Fluticasone/vilanterol	100 µg/ 25 µg	100 µg/ 25 µg	1 × 100 µg/ 25 µg	365	365 × 100 µg/ 25 µg
- of LAMA and LABA					
Tiotropium/olodaterol	5 µg/5 µg	5 µg/5 µg	2 × 2.5 µg/ 2.5 µg	365	730 × 2.5 µg/2.5 µg
Indacaterol/glycopyrronium	100 µg/ 50 µg	100 µg/ 50 µg	1 × 100 µg/ 50 µg	365	365 × 100 µg/50 µg
Umeclidinium/vilanterol	62.5 µg/ 25 µg	62.5 µg/ 25 µg	1 × 62.5 µg/ 25 µg	365	365 × 62.5 µg/25 µg
Aclidinium/formoterol	343 µg/ 12 µg	686 µg/ 24 µg	2 × 343 µg/ 12 µg	365	730 × 343 µg/12 µg
- of ICS and LABA and LAMA					
Beclometasone/formoterol/glycopyrronium	200 µg/12 µg/ 20 µg	400 µg/24 µg/ 40 µg	4 x 100 µg/ 6 µg/ 10 µg	365	1460 x 100 µg/6 µg/10 µg

Costs:

To calculate the cost of medicines, the required number of single doses of a particular potency was first determined on the basis of consumption. Based on the determined number of single doses required, the medicinal product costs were then calculated based on the costs per package (largest in each case) after deduction of the statutory rebates. In order to improve comparability, the costs of the medicinal products were approximated both on the

basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Section 130a SGB V (paragraph 1, 1a, 3a) and Section 130, paragraph 1 SGB V.

For the beta-2 sympathomimetics and the inhaled corticosteroids, the respective fixed amount was used.

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed				
Fluticasone furoate/umeclidinium/vilanterol	€ 264.73	€ 1.77	€ 14.05	€ 248.91
Appropriate comparator therapy - LABA and LAMA and ICS				
long-acting beta-2 sympathomimetics (LABA)				
Salmeterol[10]	€ 80.67	€ 1.77	€ 5.51	€ 73.39
Olodaterol[10]	€ 83.67	€ 1.77	€ 5.75	€ 76.15
Formoterol[10]	€ 83.67	€ 1.77	€ 5.75	€ 76.15
Indacaterol[10] (150 µg)	€ 56.86	€ 1.77	€ 3.63	€ 51.46
Indacaterol[10] (300 µg)	€ 85.05	€ 1.77	€ 5.86	€ 77.42
long-acting anticholinergics (LAMA)				
Tiotropium[9]	€ 143.23	€ 1.77	€ 6.28	€ 135.18
Aclidinium	€ 121.36	€ 1.77	€ 0.00	€ 119.59
Glycopyrronium	€ 169.68	€ 1.77	€ 8.79	€ 159.12
Umeclidinium	€ 117.91	€ 1.77	€ 5.92	€ 110.22
Inhaled corticosteroids (ICS)				
Beclometasone[10] 0.2 mg	€ 65.52	€ 1.77	€ 4.31	€ 59.44
Fluticasone[10] 250 µg	€ 51.68	€ 1.77	€ 3.22	€ 46.69
Fixed combinations				
- of ICS and LABA				
Beclometasone/formoterol[11]	€ 164.64	€ 1.77	€ 12.15	€ 150.72
Budesonide/formoterol[11] (320 µg/9 µg)	€ 148.32	€ 1.77	€ 10.86	€ 135.69
Salmeterol/fluticasone[11]	€ 133.59	€ 1.77	€ 9.70	€ 122.12
Fluticasone/vilanterol[11]	€ 104.99	€ 1.77	€ 7.44	€ 95.78
- of LAMA and LABA				
Tiotropium/olodaterol	€ 204.43	€ 1.77	€ 10.71	€ 191.95
Indacaterol/glycopyrronium	€ 207.83	€ 1.77	€ 0.00	€ 206.06
Umeclidinium/vilanterol	€ 155.07	€ 1.77	€ 7.98	€ 145.32
Aclidinium/formoterol	€ 204.43	€ 1.77	€ 10.71	€ 191.95

[10] Fixed amount Level II.

[11] Fixed amount Level III.

Designation of the therapy	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
- of ICS and LABA and LAMA				
Beclometasone/formoterol/glycopyrronium	€ 268.19	€ 1.77	€ 14.24	€ 252.18

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2019

Other services covered by SHI funds:

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 additionally required SHI services had to be taken into account.

3. Bureaucratic costs

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

In a letter dated 15 February 2018, received on 15 February 2018, the pharmaceutical company requested consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on, among other things, the question of appropriate comparator therapy. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 April 2018. The consultation meeting took place on 4 May 2018.

On 15 November 2018, the pharmaceutical company submitted a dossier for the benefit assessment of fluticasone furoate/umeclidinium/vilanterol to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 15 November 2018 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 fluticasone furoate/umeclidinium/vilanterol.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 February 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 February 2019. The deadline for submitting written statements was 8 March 2019.

The oral hearing was held on 26 March 2019.

By letter dated 26 March 2019, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 12 April 2019.

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 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 24 April 2019, and the proposed resolution was approved.

At its session on 2 May 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	24 April 2018	Determination of the appropriate comparator therapy
Working group Section 35a	20 March 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	26 March 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 April 2019 17 April 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal product	24 April 2019	Concluding discussion of the proposed resolution
Plenum	2 May 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 May 2019

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

Prof Hecken