IQWiG Reports – Commission No. A18-79

Fluticasone furoate/ umeclidinium/vilanterol (COPD pretreated with LABA + LAMA) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Fluticasonfuroat/Umeclidinium/Vilanterol (mit LABA + LAMA vorbehandelte COPD) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 February 2019). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the fixed-dose drug combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 November 2018.

Research question

The aim of this report is to assess the added benefit of FF/UMEC/VI as maintenance therapy compared with the appropriate comparator therapy (ACT) in adults with moderate to severe chronic obstructive pulmonary disease (COPD) who are inadequately controlled with a combination of a long-acting beta-2 sympathomimetic (LABA) and a long-acting muscarinic receptor antagonist (LAMA).

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2[2]: Research question of the benefit assessment of FF/UMEC/VI

Research question	Indication	ACT[a]
1	Maintenance therapy in adults with moderate to severe COPD who are inadequately controlled with a combination of LABA and LAMA (i.e. continue to have symptoms)	Individualized therapy optimization of existing LABA + LAMA therapy with LABA + LAMA and, if appropriate, ICS
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Joint Federal Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 sympathomimetic; LAMA: long-acting muscarinic receptor antagonist; UMEC: umeclidinium; VI: vilanterol		

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided in the company's dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for assessing any added benefit.

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

Results

The company assessed the added benefit on the basis of 2 RCTs – the IMPACT and the FULFIL studies. These studies are unsuitable for deriving an added benefit of FF/UMEC/VI compared with the ACT.

IMPACT study

The IMPACT study is a 3-arm, double-blind RCT comparing the fixed-dose triple combination FF/UMEC/VI with the fixed-dose dual combinations FF/VI and UMEC/VI. At enrolment into the study, patients had to present with severe to very severe airway obstruction ($FEV_1 < 50\%$) and ≥ 1 episode of moderate or severe exacerbation occurring within the last 12 months prior to screening, or moderate airway obstruction ($50\% \leq FEV_1 < 80\%$) and ≥ 2 episodes of a moderate or ≥ 1 episode of severe exacerbation occurring within the last 12 months prior to screening.

The IMPACT study is unsuitable for deriving an added benefit for the following reasons.

In the UMEC/VI arm of the IMPACT study, the ACT was not implemented since treatment with UMEC/VI had not been individualized for the patients in this arm. The switch to UMEC/VI presumably does not constitute an optimization of therapy in many cases. About 2/3 of the patients had ≥ 2 moderate or ≥ 1 severe exacerbation in the year before the screening and would be classified as GOLD category D. If symptoms and exacerbations persist despite therapy with LABA + LAMA, the guidelines for these patients recommend escalation to a triple combination of ICS + LAMA + LABA.

In the FF/VI arm of the IMPACT study – as in the UMEC/VI arm – the ACT was not implemented. This was because the patients were assigned to a fixed-dose treatment regimen – therapy thus not being individualized – and because the study medication contained no LAMA component. It can be assumed here as well that some of the patients would have been indicated for escalation to triple therapy consisting of ICS + LAMA + LABA due to airway obstruction and the history of exacerbations.

FULFIL study

The FULFIL study is a 2-arm, double-blind RCT comparing the fixed-dose triple combination FF/UMEC/VI with the fixed-dose dual combination of budesonide/formoterol. At enrolment into the study, patients had to present with severe to very severe airway obstruction ($FEV_1 < 50\%$) or moderate airway obstruction ($50\% \leq FEV_1 < 80\%$). The latter scenario additionally required ≥ 2 moderate exacerbations or ≥ 1 severe exacerbations occurring within 12 months prior to the screening.

The FULFIL study is unsuitable for deriving an added benefit for the following reasons.

About half of the patients in the FULFIL study had ≥ 2 moderate or ≥ 1 severe exacerbation in the year prior to the screening (GOLD group D). If symptoms and exacerbations persist despite

therapy with LABA + LAMA, the guidelines for these patients recommend escalation to triple combination consisting of ICS + LAMA + LABA. According to the guidelines, patients who had ≤ 1 moderate and no severe exacerbation in the year prior to the screening should preferably be treated with LAMA + LABA, but without ICS. Therefore, the ICS in the control arm (BUD/FOR) of the FULFIL study was likely not indicated in a considerable percentage of patients, while treatment in another subset of patients was inadequate due to the non-escalation to triple therapy.

Consequently, the ACT was not implemented in the comparator arm of the FULFIL study – as in the IMPACT study – since the patients were assigned to a fixed-dose treatment regimen, i.e. therapy was not individualized. Another reason why the ACT was not implemented was that the study drug contained no LAMA component.

Summary

The company's dossier presented no data suitable for assessing an added benefit of FF/UMEC/VI for the therapeutic indication. Consequently, there is no hint of an added benefit of FF/UMEC/VI in comparison with the ACT. An added benefit is therefore not proven.

Ongoing INTREPID study

The company is currently conducting the INTREPID study until December 2019 to compare a triple combination consisting of FF/UMEC/VI with another individualized triple combination consisting of ICS + LAMA + LABA. The INTREPID study may be suitable for assessing an added benefit since the study treatment in the control arm approximates individualized treatment optimization considerably more closely than that of the IMPACT and FULFIL studies.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of FF/UMEC/VI.

[3] Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Maintenance therapy in adults with moderate to severe COPD who are inadequately controlled (i.e. continue to have symptoms) with a combination of LABA and LAMA	Individualized therapy optimization of existing LABA + LAMA therapy with LABA + LAMA and, if appropriate, ICS	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Joint Federal Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 sympathomimetic; LAMA: long-acting muscarinic receptor antagonist; UMEC: umeclidinium; VI: vilanterol		

The G-BA decides on the added benefit.

Note:

An addendum (A19-27) to dossier assessment A18-79 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-79-fluticasone-furoate-umeclidinium-vilanterol-copd-benefit-assessment-according-to-35a-social-code-book-v.11002.html.