No added benefit proven for umeclidinium/vilanterol in COPD

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The drug combination umeclidinium/vilanterol (trade name Anoro) has been approved since May 2014 for adults with chronic obstructive pulmonary disease (COPD). In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this drug combination offers an added benefit over the appropriate comparator therapy.

According to the findings, an added benefit is not proven: For patients with moderate COPD severity and patients with fewer than two acute flare-ups (exacerbations) per year, evaluable data were only available on the outcomes "dyspnoea" and "health-related quality of life". However, these data showed no differences in comparison with tiotropium. For higher severity grades with more exacerbations, the drug manufacturer presented no evaluable analyses at all.

G-BA specified tiotropium as appropriate comparator therapy

In COPD, the lungs are permanently damaged, and the airways (bronchi) are continuously narrowed. This makes breathing more difficult. The symptoms can be relieved by drugs called bronchodilators, which widen the airways. Long-acting bronchodilators like umeclidinium and vilanterol are used on a long-term basis (with a dry powder inhaler) to relieve symptoms like dyspnoea in various ways.

The Federal Joint Committee (G-BA) distinguished between two constellations with regard to the appropriate comparator therapy: In adult patients with COPD severity grade II (moderate severity) and grades III/IV with fewer than two exacerbations per year, long-acting beta-2 sympathomimetics (formoterol, salmeterol) and/or long-acting anticholinergics (tiotropium) are to be used. In higher COPD severity grades (grade III or higher) with more than one exacerbation per year, inhaled corticosteroids (ICS) are to be used in addition.

Data only for patients with few exacerbations

The manufacturer only specified a comparator therapy (tiotropium) for the treatment of patients with moderate severity and patients with few exacerbations, and only claimed an added benefit for its fixed combination in comparison with this comparator therapy.

The manufacturer used three randomized controlled trials for the direct comparison of umeclidinium/vilanterol with tiotropium (DB2113360, DB2113374 and ZEP117115). In the studies, concomitant treatment with ICS was also allowed for moderate severity grades. However, this does not concur with the appropriate comparator therapy specified by the G-BA. Hence, only the data of approximately half of the study participants could be used for the assessment of the added benefit.

The analyses on the basis of the total population presented by the company were inadequate. IQWiG therefore used the analyses for the patients without concomitant ICS treatment as an approximation for patients with moderate COPD severity grades and patients with fewer than two exacerbations per year.

Lack of analyses for most outcomes

In moderate severity grades and patients with few exacerbations, the

dossier contained no evaluable analyses on the outcome "mortality", most COPD symptoms, the frequency of moderate and severe exacerbations and side effects. There were evaluable results with regard to the symptom "dyspnoea" and health-related quality of life, but these showed no statistically significant differences between the treatment groups.

Since evaluable results on outcomes of mortality and morbidity and of all side effects are lacking, greater harm from umeclidinium/vilanterol cannot be excluded either. Hence no conclusive balancing can be conducted on the added benefit. An added benefit of the fixed combination of umeclidinium/vilanterol versus the appropriate comparator therapy is therefore not proven for patients with moderate COPD severity grades and patients with fewer than two exacerbations per year.

No analyses for higher severity grades

The manufacturer specified no comparator therapy for the second constellation in higher severity grades with more exacerbations and also claimed no added benefit: From the company's point of view, not enough patients with COPD grades III/IV with more than one exacerbation per year were included in the three studies cited.

In contrast to patients with few exacerbations, data extraction as an approximation for patients with higher severity grades and more exacerbations was not possible using the manufacturer's analyses. Since evaluable analyses are lacking, an added benefit of umeclidinium/vilanterol is also not proven for these patients.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit

assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

More information: An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the website www.gesundheitsinformation.de, published by IQWiG, provides easily understandable and brief German-language information on umeclidinium/vilanterol.

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