Minor added benefit of indacaterol/glycopyrronium in COPD

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The drug combination indacaterol/glycopyrronium (trade name: Ultibro Breezhaler, Xoterna Breezhaler) has been approved since September 2013 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, the drug combination is better at relieving breathing difficulties (dyspnoea) than a combination treatment with tiotropium and formoterol. However, this only applies to patients who do not yet need inhaled corticosteroids because they have no more than 2 acute flare-ups (exacerbations) per year. Furthermore, there is an indication that the severity of the disease may influence the treatment result, and hence is a so-called "effect modifier". Hence overall, there is only a hint of a minor added benefit for patients with COPD grade 2. In contrast, there is an indication of a minor added benefit for patients with COPD grade 3 and no more than 2 exacerbations per year.

Due to a lack of relevant data, an added benefit of indacaterol/glycopyrronium is not proven for adults with symptoms at later stages of disease (COPD grades 4 and 3/4 with more than 2 exacerbations per year).

Tiotropium with formoterol as 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 indacaterol and glycopyrronium are used on a long-term basis (with a dry powder inhaler) and relieve symptoms like dyspnoea in various ways.

The appropriate comparator therapy specified by the Federal Joint Committee (G-BA) takes into account the graded scheme of the most recently effective German National Care Guideline COPD: From grade 2, long-acting beta-2 sympathomimetics (formoterol, salmeterol) and/or long-acting anticholinergics (tiotropium bromide) should be used; from grade 3/4 with more than 2 exacerbations per year, inhaled corticosteroids (ICS) should be used in addition.

The drug manufacturer chose formoterol in combination with tiotropium bromide (tiotropium for short) as appropriate comparator therapy. In its dossier however, it did not consider the conditions specified by the G-BA for the use of ICS for the inclusion of studies.

Added benefit not proven in most severe symptoms

The manufacturer used a randomized controlled trial (QUANTIFY - QVA149ADE01) for the direct comparison of indacaterol/glycopyrronium with the comparator therapy: 934 adults with COPD were included in the 6-month study.

Patients who had already received ICS treatment before enrolment continued this treatment. However, apart from a few exceptions, the study participants did not receive this treatment according to the

specifications for the appropriate comparator therapy. 41% of the study participants therefore had to be excluded from the assessment. Hence relevant data were only available for a part of the therapeutic indication of indacaterol/glycopyrronium.

No differences in most outcomes

There were no significant differences between the treatment groups with regards to mortality, side effects and quality of life. Hence an added benefit is not proven for these patient-relevant outcomes.

The assessment of COPD symptoms and the associated impairments in daily life conducted on the basis of a questionnaire (COPD Assessment Test, CAT) showed only marginal differences between the 2 study groups. No added benefit of the drug combination can be derived from this.

The proportion of moderate and severe exacerbations in the study participants did not differ between the treatment groups. Adults with COPD grade 3 who were treated with indacaterol/glycopyrronium had marginally fewer moderate exacerbations, but the same number of severe exacerbations as the comparator group. There were no relevant differences between the study groups in COPD grade 2. Hence an added benefit is also not proven for these outcomes.

Fewer breathing difficulties

The Transition Dyspnoea Index (TDI) uses a questionnaire to measure the severity of dyspnoea, the main symptom of COPD. The patient's TDI score at the start of the study served as comparison.

According to the TDI, adults with COPD grade 2 and grade 3 with no

more than 2 exacerbations per year who were treated with indacaterol/glycopyrronium had fewer breathing difficulties than patients under treatment with tiotropium and formoterol. A minor added benefit of the new drug combination can be derived from this.

However, the severity of the disease is an effect modifier and may influence the treatment result. Hence overall, in the treatment with indacaterol/glycopyrronium, there is a hint of a minor added benefit for adults with COPD grade 2. For adults with COPD grade 3 with no more than 2 exacerbations per year, there is an indication of a minor added benefit.

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.

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