Added benefit of aclidinium bromide is not proven

January 30 2013

The drug aclidinium bromide (trade names Eklira, Bretaris) has been approved since October 2012 for widening the narrowed airways of adults with chronic-obstructive pulmonary disease (COPD). The German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined the added benefit of the drug pursuant to the "Act on the Reform of the Market for Medicinal Products" (AMNOG). No proof of an added benefit of aclidinium bromide compared with the appropriate comparator therapy (ACT) can be inferred from the data in the drug manufacturer's dossier.

No robust results were submitted by the manufacturer in its dossier: for the direct comparison, there were no studies of an adequate duration. The data for the indirect comparison were incomprehensible for several reasons. Therefore the added benefit is not proven.

Tiotropium bromide as the appropriate comparator therapy

In COPD the lungs are permanently damaged and the airways are constantly narrowed. This makes breathing difficult. Aclidinium bromide (aclidinium for short) is a "bronchodilator" approved for long-term therapy. It inhibits the body's own substance acetylcholine which causes the bronchial muscles to tense up in COPD. The drug aclidinium, in the form of a powder, is breathed in using a special inhaler (Genuiar).

The ACT specified by the Federal Joint Committee (G-BA) takes account of the graded treatment scheme of the current National Care Guidelines for COPD: from Stage II of the disease, long-acting beta-2 sympathomimetics (formoterol, salmeterol) and/or long-acting anticholinergics (tiotropium bromide) are to be used; from Stage III/IV, if there are more than 2 severe attacks (exacerbations) per year, inhaled corticosteroids (ICS) are recommended in addition. The manufacturer followed these requirements and chose tiotropium bromide (tiotropium for short) as ACT.

Study duration too short for direct comparison

Since aclidinium is a long-term treatment, a reliable benefit assessment requires studies that last for at least 6 months. However, for the direct comparison of aclidinium with tiotropium, the manufacturer submitted 2 studies that only lasted for 2 and 6 weeks respectively. The dossier thus contained no studies relevant for the direct comparison.

Placebo studies for indirect comparison

For the indirect comparison, the manufacturer used studies that compared aclidinium and tiotropium with a dummy drug (placebo) in each case. But of a total of 24 studies (3 on aclidinium, 21 on tiotropium) only 14 were suitable for the assessment, because the others had lasted for less than 6 months.

Results for indirect comparison incomprehensible

When comparing the submitted results on the placebo studies with the original sources, IQWiG found substantial differences: on the one hand, some of the manufacturer's information did not match the corresponding original data. On the other hand, it was often unclear whether data

emanated from the manufacturer or from another source and how they had been calculated. Much of the information in the manufacturer's dossier (especially about patient numbers and confidence intervals) could not be traced in the original sources.

Due to these deficiencies, it was impossible to check and therefore also to interpret the results presented in the dossier for almost all outcomes regarding benefit. In addition, the manufacturer repeatedly did not consider study results on relevant outcomes (exacerbations, mortality, quality of life), although they were to be found in the original sources. Because of these deficiencies, an added benefit of aclidinium on the basis of the manufacturer's dossier is not proven.

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.

Provided by Institute for Quality and Efficiency in Health Care