Emtricitabine/tenofovir alafenamide in HIV infection: Added benefit not proven

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The drug combination emtricitabine/tenofovir alafenamide is approved in combination with other antiviral agents for the treatment of adults and adolescents infected with human immunodeficiency virus type 1 (HIV-1). In an early benefit assessment, the German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined whether in these patients this combination offers advantages over the appropriate comparator therapy. According to the findings, such an added benefit is not proven: No data were available for two of four research questions; the studies submitted for the third research question deviated from the appropriate comparator therapy; greater harm for certain patients was shown in the fourth research question.

No relevant data for adolescents

The Federal Joint Committee (G-BA) differentiated between four groups of patients according to age and treatment status. Two groups - pretreated and treatment-naive adolescents - were not considered in the drug manufacturer's dossier. IQWiG did not follow the manufacturer's justification that the guideline recommendations did not differentiate between adolescents and adults and that adolescents constituted less than one per cent of the target population. A search for corresponding studies in adolescents returned no results, however. It was therefore concluded that an added benefit of the emtricitabine/tenofovir alafenamide combination in comparison with the appropriate comparator therapy is not proven for treatment-naive or for pretreated adolescents.

Appropriate comparator therapy not adhered to

The dossier also contained no suitable data for treatment-naive adults. According to the G-BA, in the comparator arm, they were to be treated with NRTI backbone therapy, i.e. with two nucleoside reverse transcriptase inhibitors, and with the same third combination partner that was also used in the intervention arm together with emtricitabine/tenofovir alafenamide: either efavirenz or rilpivirine or dolutegravir. Instead, the manufacturer submitted studies in which the new combination was combined with elvitegravir/cobicistat in the test arm, and the NRTI backbone therapy emtricitabine/tenofovir disoproxil was combined with elvitegravir/cobicistat in the comparator arm. The third combination partner (elvitegravir/cobicistat) therefore did not comply with the appropriate comparator therapy.

The manufacturer supported this with three arguments, which were not followed by IQWiG, however. According to the first argument, the third combination partner is not methodologically relevant for a comparison between two NRTI backbone therapies. An effect modification by the third partner cannot be excluded, however; corresponding subgroup analyses would be required for this.

Unproven inequivalence does not mean proof of equivalence

According to the second argument, the combination elvitegravir/cobicistat is at least equivalent to one of the three combination partners named by the G-BA, namely efavirenz. According to the manufacturer, this can be inferred from a G-BA decision in which "no sufficient proof of an added benefit or lesser benefit" of a combination with elvitegravir/cobicistat in comparison with a combination with efavirenz was found. However, unproven

inequivalence does not mean that equivalence is established. The comparison on which the G-BA decision was based actually showed disadvantages of elvitegravir/cobicistat in comparison with efavirenz for individual outcomes.

According to the third argument, the use of elvitegravir/cobicistat as third combination partner is appropriate because those comparator therapies are to be preferred for which the G-BA has already established a patient-relevant benefit. In contrast to rilpivirine and dolutegravir, this is not the case with elvitegravir/cobicistat, however.

No data for adults with indication for a treatment switch

The appropriate comparator therapy for pretreated adults was individual antiretroviral therapy. The manufacturer differentiated between patients with indication for a treatment switch, e.g. due to treatment failure or side effects, and those for whom the ongoing treatment can be continued in the comparator arm. No data were available for the first group; an added benefit of emtricitabine/tenofovir alafenamide in comparison with the appropriate comparator therapy for this group is therefore not proven.

For the group without indication for a treatment switch, the manufacturer submitted two principally suitable studies, in which some patients with indication for a treatment switch were possibly also included, however. This made the interpretation of the results more difficult.

More nervous system disorders

The analyses provided no hints of an added benefit of the new

combination in comparison with continuation of ongoing treatment for mortality, morbidity and health-related quality of life. Negative effects were shown in the outcome category of side effects, however, namely in the outcome "nervous system disorders": With a so-called boosted protease inhibitor as third combination partner, there was a hint (extent: "minor"), with other partners even proof (extent: "considerable") of greater harm of the new combination.

Overall, an added benefit of emtricitabine/tenofovir alafenamide in comparison with the appropriate comparator therapies is not proven for any of the four research questions; pretreated adults without indication for a treatment switch can expect greater harm from the combination than from continuation of their ongoing treatment.

G-BA decides on the extent of added benefit

The dossier assessment is part of the early benefit assessment according to the Act on the Reform of the Market for Medicinal Products (AMNOG) supervised by the G-BA. After publication of the dossier assessment, the G-BA conducts a commenting procedure and makes a final decision on the extent of the added benefit.

An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the Website gesundheitsinformation.de, published by IQWiG, provides easily understandable German-language information.

More English-language information will be available soon (Sections 2.1 to 2.7 of the dossier assessment as well as subsequently published health information on informedhealth.org).

More information: www.iqwig.de/download/A16-30_E … ertung-35a-SGB-V.pdf