Tenofovir alafenamide in chronic hepatitis B: Added benefit not proven, data incomplete

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The antiviral drug tenofovir alafenamide (TAF) has been used since 2015 in different combinations for the treatment of HIV and has already been subject to 3 early benefit assessments for this therapeutic indication. It has now also been approved for the treatment of adults and adolescents with chronic hepatitis B. The German Institute for Quality and Efficiency in Health Care (IQWiG) now examined in a further early benefit assessment whether the drug offers an added benefit for these patients.

In its dossier, the drug manufacturer presented no data for treatment-naive or pretreated adolescents aged 12 and older. The data from 2 studies presented by the manufacturer for treatment-naive or pretreated adults were incomplete to a major extent and for this reason alone were unsuitable for a benefit assessment. In addition, the delineation between treatment-naive and treatment-experienced patients was contradictory, and the appropriate comparator therapy was partly not implemented. Hence an added benefit in comparison with the respective appropriate comparator therapy is not proven for any of the 4 patient groups mentioned.

What does "pretreated" mean?

The Federal Joint Committee (G-BA) differentiated between 4 groups of patients by age (adults or adolescents) and by antiviral pretreatment (treatment-naive or treatment-experienced) and specified corresponding

appropriate comparator therapies.

For adults, the TAF manufacturer presented data from 2 studies. Both studies investigated treatment-naive as well as treatment-experienced patients so that the manufacturer analysed subgroups for the respective research questions.

According to its classification, all participants who had not received any oral medication were considered treatment-naive. Numerous study participants who had already been treated with interferon using other forms of administration were allocated to the group of treatment-naive patients, which contradicts the G-BA's specification. In addition, some patients with oral pretreatment were also allocated to the treatment-naive group, and some patients without oral pretreatment were allocated to the treatment-experienced group, without the manufacturer explaining this approach. The creation of patient groups was therefore inadequate.

Strong selection of submitted study results

Above all, however, the manufacturer presented only incomplete data for the outcome category "specific adverse events" for the subpopulations. In particular, data were missing on events for which the overall studies showed notable differences to the disadvantage of the new drug.

Thomas Kaiser, Head of IQWiG's Drug Assessment Department, says: "This is an exceptional case because whole tables were evidently shortened. As an example in the assessment, we have shown this for one of the study data tables, of which we only received 3 of 38 pages. The situation was similar for the other tables on specific adverse events."

Complete data are essential for an assessment according to the methods of evidence-based medicine. If the reporting is selective, the data cannot

be reliably interpreted.

More frequent nervous system disorders cannot be excluded

"It is not up to the manufacturer to decide which adverse events are of interest. To evaluate this is an important part of our statutory duty", Thomas Kaiser explains.

In the present case, the manufacturer derived an added benefit of its drug in comparison with other antiviral treatment options mainly from an "improved tolerability profile". And yet it cannot be excluded that TAF even has lesser benefit because certain adverse events, particularly nervous system disorders, are potentially more common. Particularly in view of the fact that these diseases occurred more frequently under a previously assessed drug combination with TAF in HIV treatment, complete data submission and particular diligence in the analysis would have been required here.

Appropriate comparator therapy not implemented

For the group of treatment-experienced adults, the study data were unsuitable for another reason: The appropriate comparator therapy was not implemented. Instead of an antiviral therapy specified for the individual patient, all participants received a uniform treatment regimen. In addition, the manufacturer presented no data at all for adolescents, neither for treatment-experienced adolescents nor for adolescents without antiviral pretreatment.

In the overall consideration, an added benefit of TAF in comparison with the respective appropriate comparator therapy is not proven for any of the 4 patient groups. "This is particularly unfortunate because this is

the first drug in several years to be approved for the treatment of hepatitis B", says Thomas Kaiser.

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.

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