Fidaxomicin in Clostridium difficile infection: Added benefit not proven

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The antibiotic fidaxomicin (trade name: Dificlir) has been approved in Germany since December 2011 for the treatment of adults who have diarrhoea caused by *Clostridium difficile*. 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 the added benefit of fidaxomicin in comparison with current standard therapy. According to this, there is currently no proof of an added benefit. The manufacturer did not submit any studies on non-severe cases. It cited studies on severe courses of disease and recurrences, but did not process the results in a way that would make it possible to draw reliable overall conclusions on benefit and harm of fidaxomicin.

G-BA distinguished between three treatment situations

For this benefit assessment, the Federal Joint Committee (G-BA) distinguished between three treatment situations, and hence also specified different drugs as appropriate comparator therapy: in courses of the disease that were not severe, but required treatment, fidaxomicin was to be compared with the antibiotic metronidazole; in severe cases and in patients with recurrence, with vancomycin, another antibiotic.

No studies on comparison with metronidazole

Results of two randomized controlled trials (RCTs), both approval studies on fidaxomicin, were available for IQWiG's assessment (studies 101.1.C.003 and 101.1.C.004). In these studies, fidaxomicin was tested against the drug vancomycin in patients with all courses of the disease, i.e. including patients who were not severely affected.

Moreover, the manufacturer did not cite any additional studies for patients with non-severe course of the disease, in whom fidaxomicin was to be compared with metronidazole. So no data were available for this appropriate comparator therapy. Hence an added benefit for this subpopulation is not proven - however, this was not claimed by the manufacturer either.

Severe cases and recurrences: advantage of fidaxomicin in global cure

The two approval studies provided usable data on the outcome "global cure" for the two subpopulations "patients with severe course of disease" and "patients with recurrence". According to these studies, patients treated with fidaxomicin have better chances of cure than those treated with vancomycin. Here IQWiG derives a proof.

Data on side effects were not analysed appropriately

Side effects were also recorded in both approval studies. However, the manufacturer did not process these data in an appropriate way: The dossier contained information on severe adverse events only for the total study population, including non-severe cases. The manufacturer failed to analyse the data separately for the subpopulation defined by the G-BA. It cannot be excluded that, in a severe course of disease and recurrences, severe side effects are more frequent under fidaxomicin treatment than under vancomycin treatment.

Overall, the pharmaceutical company did not provide sufficient proof in its dossier that the positive effects (global cure) outweigh the negative effects (side effects). Hence an added benefit of fidaxomicin is not proven also in comparison with vancomycin on the basis of the manufacturer's dossier.

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.

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 and brief German-language information on fidaxomicin.

The G-BA website contains both general English-language information on benefit assessment pursuant to §35a Social Code Book V and specific German-language information on the assessment of fidaxomicin.

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