Aflibercept in macular oedema: Added benefit not proven

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For the third time in one year, the German Institute for Quality and Efficiency in Health Care (IQWiG) dealt with the drug aflibercept. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the Institute now examined whether aflibercept (trade name: Eylea) offers an added benefit over the appropriate comparator therapy in visual impairment due to macular oedema following occlusion of the central retinal vein. An added benefit could not be derived from the dossier because in the studies cited by the drug manufacturer, both aflibercept and the comparator therapy were not used in accordance with their approvals.

Indirect comparison between aflibercept and ranibizumab

Macular oedema is a retention of fluid in the macular area of the eye, which leads to blurring in the field of vision. If this is caused by occlusion of the central retinal vein, it can be attempted to improve visual acuity by injecting growth factor inhibitors like aflibercept. ´

The Federal Joint Committee (G-BA) specified either a dexamethasone intravitreal implant or the drug ranibizumab, another growth factor inhibitor, as appropriate comparator therapy. In its dossier, the pharmaceutical company presented three randomized controlled trials, on the basis of which it conducted an indirect comparison between aflibercept and ranibizumab: In two studies, aflibercept was compared

with sham injections, and in the third study, sham injections were compared with ranibizumab.

Patients did not receive approval-compliant treatment

However, both drugs were not used in accordance with their approvals in the studies. The Summaries of Product Characteristics of aflibercept and ranibizumab are unambiguous: After the first injection, treatment is to be continued at monthly intervals until the functional and morphological assessment or visual acuity is stable for three consecutive monthly assessments performed while on treatment. If needed, treatment can then be continued at larger intervals. If there is no improvement over the course of the first three injections, however, continued treatment is not recommended.

Extent of deviation from approval could not be estimated

All three studies used different approaches: Independent from the changes in the individual outcomes, six planned injections were administered in 20 weeks. The data submitted also contained no information on the proportion of patients who received injections despite stable outcomes or who did not respond to treatment, i.e. in whom there was no improvement after the first three injections. It therefore remains unclear how many patients received injections that were unnecessary either because of stable improvement or because of treatment failure and that therefore contravened the approval. ´

On the basis of these data it cannot be estimated to what extent treatment in the studies deviated from the stipulations of the approval. Hence the indirect comparison conducted in the dossier was unsuitable for proving an 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.

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 aflibercept.

The G-BA website contains both general English-language information on benefit assessment pursuant to §35a Social Code Book (SGB) V and specific German-language information on the assessment of aflibercept in macular oedema.

Provided by Institute for Quality and Efficiency in Health Care