Alirocumab in hypercholesterolaemia or mixed dyslipidaemia: Added benefit not proven

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The drug alirocumab (trade name: Praluent) has been approved since September 2015 for adults with hypercholesterolaemia or mixed dyslipidaemia whose cholesterol levels are not adequately lowered by diet and other drugs. It can also be used if statins are not a treatment option or are not tolerated because of adverse events.

The German Institute for Quality and Efficiency in Health Care (IQWiG) recently examined the added benefit of a similar drug pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG): evolocumab. The Federal Joint Committee (G-BA) now commissioned the Institute to also assess the drug manufacturer dossier on alirocumab. An added benefit in comparison with the appropriate comparator therapies is also not proven for this drug.

Monoclonal antibodies aim to lower LDL levels

Hypercholesterolaemia is diagnosed when the LDL cholesterol levels in the blood are high. In mixed dyslipidaemia, triglyceride levels may also be elevated. Untreated, both disorders can lead to cardiovascular disease such as coronary heart disease or arteriosclerosis if the values are very high.

Standard treatment options include diet in combination with lipid-lowering drugs (such as statins) or, if drugs and diet are insufficient,

LDL apheresis, a procedure similar to dialysis, in combination with drug treatment. In LDL apheresis, LDL cholesterol is eliminated from the blood. For some patients however, these measures are insufficient.

Drugs known as PCSK9 inhibitors, such as alirocumab or evolocumab, help remove LDL cholesterol in the liver. The enzyme PCSK9 binds to LDL receptors of the liver cells instead of LDL cholesterol, causing the receptors to be broken down, thus increasing the cholesterol level in the blood. If a substance such as alirocumab blocks this enzyme, the number of LDL receptors is increased and cholesterol levels can drop.

G-BA defined three research questions

The G-BA specified different appropriate comparator therapies for three patient populations: In patients who tolerate statins, but do not achieve their target cholesterol levels even on the their maximum tolerated statin dose, alirocumab in combination with a statin and, if applicable, further lipid-lowering drugs was to be compared with a maximum tolerated drug and dietary treatment for lowering lipid levels.

In patients for whom statin treatment is not an option alirocumab was to be compared with a different lipid-lowering drug as monotherapy. And for patients for whom drug and dietary options for lowering lipid levels are exhausted LDL apheresis was to be the appropriate comparator therapy.

Wrong population, wrong comparator therapies, studies too short

None of the twelve studies in total cited by the manufacturer in its dossier for these three research questions answers the relevant research questions of the early benefit assessment. Firstly, part of the patients had

received no prior therapy with their maximum tolerated dose of statins in numerous studies on the first research question. This is a prerequisite for treatment with alirocumab, however.

Secondly, the appropriate comparator therapy was not adhered to in many studies, or no data were available for those study participants who corresponded to the inclusion criteria. And thirdly, some of the studies were too short, as was the case already with evolocumab. Hypercholesterolaemia and mixed dyslipidaemia are chronic diseases; alirocumab is intended for long-term treatment. Hence studies with a minimum duration of one year are required to assess benefit or harm.

Since none of the studies was relevant for the benefit assessment, there was no hint of an added benefit of alirocumab in comparison with the respective appropriate comparator therapy for any of the therapeutic indications.

G-BA decides on the extent of added benefit

This dossier assessment is part of the early benefit assessment according to 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 " http://www.gesundheitsinformation.de, published by IQWiG, provides easily understandable German-language information.

More English-language information will be available soon (Sections 2.1 to 2.6 of the dossier assessment as well as subsequently published health information on " http://www.informedhealth.org).

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More information: www.iqwig.de/download/A15-47_A … ertung-35a-SGB-V.pdf

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