Selexipag in pulmonary arterial hypertension: Added benefit not proven

October 6 2016

Selexipag (trade name: Uptravi) is approved for long-term treatment of pulmonary arterial hypertension (PAH) in adults with moderate to severe symptoms. The drug can be used either as combination therapy with other blood-pressure lowering drugs or as monotherapy in patients who are not candidates for these therapies. Selexipag has been on the market in Germany since May 2016. In an early benefit assessment, the German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined whether this drug has advantages or disadvantages in comparison with the appropriate comparator therapy.

The limitation of the comparator therapy to a specific drug and the subsequent division of the population in the dossier were inadequate. The only study cited by the drug manufacturer for one of its subpopulations compared selexipag with placebo. However, no added benefit can be inferred from such a comparison.

Hence the manufacturer presented no suitable data for the assessment of the added benefit of selexipag, and IQWiG concluded: An added benefit of selexipag in comparison with the appropriate comparator therapy is not proven.

Selective widening of vessels and inhibition of tissue growth

In PAH, the pulmonary artery is narrowed, and the heart has to work

harder to pump oxygen-poor blood through the pulmonary artery into the lungs. The permanently increased workload of the right heart chamber decreases the body's oxygen supply. The high blood pressure (hypertension) is often caused by another heart or lung disease, e.g. by chronic obstructive pulmonary disease (COPD) or a congenital heart defect.

Selexipag aims to widen the pulmonary artery and slow down the overload of the heart. The drug is approved for long-term treatment of PAH patients who have no symptoms at rest but who have slight (WHO functional class II) or marked (WHO functional class III) limitation of physical activity. These restrictions cause symptoms such as dyspnoea, tiredness, chest pain, or dizziness. Selexipag is an option as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase-5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Manufacturer deviated from appropriate comparator therapy

The Federal Joint Committee (G-BA) specified individually optimized drug treatment specified by the physician under consideration of the respective approval status as appropriate comparator therapy.

The manufacturer deviated from this specification and considered only iloprost as an option of an individual drug treatment. It did also not use individual optimization.

In addition, the manufacturer distinguished between two subpopulations: Its "subpopulation a" comprised patients for whom also iloprost is not an option, and for whom therefore only watchful waiting until worsening of the PAH is available. Its "subpopulation b" comprised patients for whom

iloprost is an option.

The limitation of the comparator therapy and the subsequent division of the population was inadequate. The Institute therefore used the appropriate comparator therapy specified by the G-BA, without division of the patient population, for the dossier assessment.

Study with placebo comparison unsuitable

The manufacturer cited a randomized controlled trial (GRIPHON) for its "subpopulation a", in which iloprost was not an option: At the start of the study, treatment in the intervention arm was expanded by administration of selexipag. There was no treatment expansion in the control arm; the patients received only placebo. In both treatment arms, it was not allowed to adjust the ongoing medication for treatment of the PAH. Iloprost was approved for about half of the patients included in the study (WHO functional class III), which contradicts the manufacturer's definition of its "subpopulation a".

The study only allowed a comparison of selexipag with placebo and was therefore unsuitable to draw conclusions on the added benefit of selexipag: The study design allowed individual adjustment of the PAH-specific treatment in case of worsening of the PAH. If the PAH worsened, however, the blinded and randomized treatment phase for the patient ended according to the study protocol.

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.

More information: www.iqwig.de/download/A16-36_S … ertung-35a-SGB-V.pdf

Provided by Institute for Quality and Efficiency in Health Care