Pirfenidone: Extent of added benefit assessed

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Pirfenidone inhibits the development of inflammation and scarring (fibrosis) in pulmonary tissue and has been approved for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) since the beginning of 2011. In an early benefit assessment in accordance with the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) has examined the extent of added benefit of pirfenidone.

Treatment with pirfenidone was compared with the appropriate comparator therapy, so-called best supportive care. This means the therapy that provides the patient with the best possible individually optimized supportive therapy to alleviate symptoms and improve quality of life (e.g. administration of additional drugs or supplemental oxygen).

IQWiG found that there was an indication that pirfenidone gave minor added benefit with respect to patients' exercise tolerance. On the other hand, greater harm has been proven: Both study discontinuations and unfavourable effects on the gastrointestinal tract were more frequent than with comparator therapy. The extent of this greater harm was classified as "minor" in each case. Harm to the skin was more frequent; IQWiG classified the extent of this as "considerable". The Institute weighed the benefits and harms and concluded that the extent of added benefit from pirfenidone should be classified as "no proven added benefit".

Manufacturers must submit dossiers for orphan drugs too

Pirfenidone (trade name Esbriet®) has been approved for the treatment of adults with mild to moderate idiopathic pulmonary fibrosis (IPF), a rare disease (orphan disease). In accordance with § 35a SGB V, an added benefit is regarded as proven if a drug for a rare disease, a so-called "orphan drug", has been approved. However, this does not mean that these drugs are not subjected to assessment. It is rather the case that they too require a dossier. This dossier must contain information about the patient groups for whom there is therapeutically important added benefit. Moreover, the manufacturer must describe the extent of the added benefit. The aim of the early benefit assessment is to establish the extent of the added benefit.

The legal ordinance on early benefit assessments specifies 6 categories for the extent of added benefit: If an added benefit is established, this may be "major", "considerable" or "minor", depending on the extent of improvement brought about by the drug. If there is added benefit, but this cannot be estimated based on the data available, this is regarded as "not quantifiable". The benefit of the drug to be assessed can also be "less than the benefit of the appropriate comparator therapy". If no added benefit can be established on the basis of the manufacturer's dossier, the ordinance specifies the category "no proven added benefit".

Studies provide data on patient-relevant outcomes

Two relevant studies with 435 (PIPF-004) and 344 (PIPF-006) patients were available for the dossier assessment. One group of study participants was treated with pirfenidone in combination with best supportive care and the comparator group was treated with best supportive care alone.

Both studies provided data for the patient-relevant outcome of mortality, as well as symptoms (morbidity) as measured by shortness of breath (dyspnoea), need for supplemental oxygen and exercise tolerance (6-min

walk test). This also applies for the outcomes "health-related quality of life" and "side effects" (adverse events).

Minor added benefit and greater harm with non-serious outcomes

No added benefit could be proven for the outcomes "mortality", "health-related quality of life" and "morbidity", as measured by dyspnoea and supplemental oxygen treatment. The patients' exercise tolerance is an aspect of morbidity and was examined using the 6-min walk test. The proportion of the participants for whom the distance walked in 6 min decreased by more than 50 m in the course of the study was statistically significantly lower under pirfenidone treatment than under best supportive care alone. As however this criterion was only specified retrospectively (post hoc), IQWiG has demoted the certainty of the results from proof to indication.

The overall comparison of the adverse events and the serious adverse events found no difference between the treatment groups.

Thus greater harm under pirfenidone treatment could not be established for these outcomes.

However, there is proof for greater harm with respect to non-serious adverse events. The proportion of patients who discontinued treatment for this reason was greater under pirfenidone. Non-serious adverse events affecting the gastrointestinal tract or the skin were also observed more frequently.

Overall assessment balances the advantages and disadvantages

The overall conclusion on the extent of added benefit must consider both the indication of added benefit and the proof of greater harm. This consideration only applies to "non-serious" outcomes. The extent of the

added benefit for exercise tolerance is classified by IQWiG as "minor". The Institute classifies the extent of harm (adverse events) as "minor" with respect to study discontinuations and the gastrointestinal tract and as "considerable" with respect to the skin.

As overall the submitted data provide no indication for added benefit from pirfenidone, the extent of the added benefit for this drug is then classified as "no proven added benefit" - as laid down in the legal ordinance.

The procedure for inferring the overall conclusion on the extent of the added benefit is a proposal from IQWiG. The G-BA will decide on the extent of the added benefit.

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