Mirabegron for overactive bladder: Added benefit not proven

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Mirabegron (trade name: Betmiga) has been approved since December 2012 for the treatment of adults with overactive bladder. 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 whether this new drug offers an added benefit over the appropriate comparator therapy specified by the Federal Joint Committee (G-BA).

Mirabegron had an advantage with regard to side effects: Dry mouth was less common in comparison with tolterodine. No added benefit could be determined for the outcomes "mortality", "morbidity" and "quality of life". As the drug manufacturer dossier contained no analyses for the total population on the patient-relevant morbidity criteria "incontinence" and "urge incontinence", it was not possible to conduct a final balancing of positive and negative effects on the added benefit. Overall, an added benefit of mirabegron is therefore not proven.

Overactive Bladder Muscles Lead to Irritable Bladder

Women and men with an overactive bladder (irritable bladder) have an increased urge to urinate, which they can hardly control or not control at all (incontinence). Having to go to the toilet more often can significantly impair daily life. People with irritable bladder have to get up at night more frequently (nocturia) and can hardly sleep through the night because of this. Women are affected more often than men.

Diagnosing overactive bladder is only possible after other causes such as urinary tract infection, neurological disorders or side effects of drugs have been excluded. Overactive bladder muscles, which contract too often, are considered to be one of the main causes. It is unknown why this happens. Mirabegron aims to relax the muscles of the bladder and relieve the urge to urinate.

G-BA Specifies Appropriate Comparator Therapy

For the treatment of adults with overactive bladder, the G-BA specified seven different drugs as appropriate comparator therapy: darifenacin, fesoterodine, propiverine, solifenacin, tolterodine and trospium chloride. These drugs belong to the group of anticholinergics, which interrupt nerve impulses in the muscles and cause the smooth bladder muscles to relax.

In the manufacturer dossier, mirabegron was compared with tolterodine. Mirabegron is a so called beta 3-adrenoceptor agonist, which activates the corresponding receptors in the muscle cells of the urinary bladder causing the smooth muscles to also relax.

Long-term Data are Essential in Long-term Treatment

IQWiG included one long-term study (179-CL-049) in the assessment, which the manufacturer had reported, but not used to derive an added benefit. As long-term therapy is necessary to treat irritable bladder, this study, with a duration of 12 months and more than 800 patients per study arm, provides the key data for the assessment of mirabegron. The results of four smaller short-term studies with a duration of 12 weeks each were used as additional information for the dossier assessment.

The average age of the mainly white study participants was between 54 and 60 years. The proportion of women was between two thirds and three quarters and therefore considerably larger.

No differences in Mortality, Morbidity and Quality of Life

There were no relevant differences between the treatment groups in severity, frequency and impairments due to the urge to urinate or in the frequency of nocturia. No added benefit of mirabegron could be derived from these results, and there were no data on further decisive aspects of morbidity: The manufacturer dossier provided no results for the total population on incontinence and urge incontinence.

There were also no statistically significant differences between the results with regard to mortality. Moreover, patients who were taking mirabegron did not assess their quality of life differently from the ones who used tolterodine. Hence there were no differences between the treatment groups with regard to these aspects either.

Advantage of Mirabegron in Side Effects

Severe side effects or discontinuations due to side effects, with approximately 5%, were as common under treatment with mirabegron as under treatment with tolterodine. However, patients under mirabegron reported fewer cases of dry mouth. This results in proof of lesser harm in non-serious side effects with the extent "considerable".

Balancing of Added Benefit not Possible

Overall, no added benefit could be derived for mirabegron because it was not possible to conduct a conclusive balancing of positive and

negative effects due to the missing data on the outcomes "incontinence" and "urge incontinence". Hence an added benefit of mirabegron versus tolterodine is not proven.

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.

Provided by Institute for Quality and Efficiency in Health Care