# Dimethyl fumarate for MS: Added benefit is not proven

August 7 2014

Dimethyl fumarate (trade name: Tecfidera) has been approved since January 2014 for adults with relapsing remitting multiple sclerosis (RRMS). 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) has examined whether this new drug for MS offers an added benefit over the appropriate comparator therapy specified by the Federal Joint Committee (G-BA). However, no added benefit can be determined, as no suitable data are available, neither for the direct nor for the indirect comparison.

## Multiple Sclerosis: New Therapeutic Indication for an Old Drug

MS is a chronic and incurable inflammatory disease of the central nervous system, which often has a relapsing course. If the symptoms disappear completely or at least largely after a relapse, the disease is referred to as "relapsing remitting" (RRMS).

Dimethyl fumarate is taken as a tablet. The exact mode of action in MS is not yet known. Fumaric acid (including dimethyl fumarate) has long been used for the treatment of moderately severe to severe types of psoriasis in patients who do not respond sufficiently to topical treatment.

## Drug Manufacturer Restricts Comparator Therapy

The G-BA specified beta-interferon (1a or 1b) or glatiramer acetate as the appropriate comparator therapy. The manufacturer chose beta-interferon 1a as the comparator therapy; however, this was restricted to a specific compound with this active agent (Rebif). But according to the G-BA, all available beta-interferon 1a compounds and thus a further compound (Avonex) should have been considered for the comparison with dimethyl fumarate.

This has no consequences for the direct comparison with the appropriate comparator therapy, as no studies were available here anyway. However, this has far-ranging consequences for the indirect comparison, which is now incomplete, as some of the available data on beta-interferon 1a were not considered.

## Approach for Indirect Comparison is Unsuitable

The manufacturer presents a so-called network meta-analysis for the indirect comparison, which includes the results from a total of 14 studies. In two studies dimethyl fumarate was compared with glatiramer acetate or placebo. The other studies were also comparisons of beta-interferon (1a or 1b) and glatiramer acetate with each other or with placebo. In such a network it is possible to compare dimethyl fumarate with beta-interferon 1a without the two drugs having been investigated in a common study. The other drugs and placebo act as so-called intermediate comparators for the indirect comparison.

In principle, this approach can be used to derive an indirect comparison for dimethyl fumarate. However, for several reasons, the indirect comparison submitted by the manufacturer is not suitable to draw conclusions on the added benefit of dimethyl fumarate:

- The data are incomplete, as the comparison with a further beta-interferon 1a (Avonex) is missing, even though this would have been possible, as the corresponding study data are available.
- The statistical model used (network meta-analysis) is not suitable, as it can lead to an incorrect evaluation of treatment effects: Non-significant differences can incorrectly appear to be significant.
- The similarity, homogeneity and consistency of the studies included as preconditions for a network meta-analysis were not adequately checked by the manufacturer. For instance, only studies investigating similar patients are allowed to be included in such a network. If, for example, the studies differ with regard to the type or severity of disease, no reliable conclusions are possible anymore. However, this basic precondition is not fulfilled in the network submitted.

An added benefit is not proven, as no suitable data are available, neither for the direct nor for the indirect comparison of dimethyl fumarate with the appropriate comparator therapy.

## 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