Added benefit of ingenol mebutate is not proven

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The drug ingenol mebutate (trade name: Picato) has been approved in Germany since November 2012 as a gel for the treatment of certain forms of actinic keratosis in adults. 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 diclofenac/hyaluronic acid gel. Such an added benefit cannot be derived from the dossier, however, as the drug manufacturer did not submit any relevant data: it did not cite any studies that directly compared ingenol mebutate with diclofenac/hyaluronic acid gel, and the method chosen by the manufacturer for an indirect comparison was unsuitable.

G-BA specified appropriate comparator therapy

Ingenol mebutate is approved for the treatment of flat, non-callous skin lesions. These are called non-hyperkeratotic and non-hypertrophic actinic keratoses. This disease can develop into a form of skin cancer (squamous cell carcinoma). The Federal Joint Committee (G-BA) specified diclofenac/hyaluronic acid gel as appropriate comparator therapy.

No direct comparative studies available

In its dossier, the manufacturer did not cite any randomized controlled trials (RCTs) that directly compared ingenol mebutate gel with diclofenac/hyaluronic acid gel. It therefore aimed for an indirect comparison. However, in the opinion of the manufacturer it was not possible to use a procedure appropriate for this, namely an adjusted indirect comparison with a common point of reference (intermediate comparator). It stated that the substances called vehicle gels that ingenol mebutate and diclofenac/hyaluronic acid were compared with in the available studies might differ in efficacy, and are therefore not comparable. These substances could therefore not be used as intermediate comparator.

Method of analysis unsuitable for indirect comparison

Instead, the pharmaceutical company used a method it called "chaining of direct comparisons". In such a comparison across several comparators it is indispensable, however, that direct comparisons exist for each link in the chain, i.e. for each pair of comparators. This condition was not fulfilled, however, as the manufacturer presented a non-adjusted comparison for one link in the chain. Hence the method of analysis was unsuitable, and its results could therefore not be used. An added benefit of ingenol mebutate is therefore 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