

IQWiG Reports – Commission No. 13-04

**Ingenol mebutate –**

**Benefit assessment according  
to § 35a Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Sections 2.1 to 2.6 of the dossier assessment “Ingenolmebutat – Nutzenbewertung gemäß § 35a SGB V” (Version 1.0; Status: 11.04.2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
G-BA	<i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee)
IQWiG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care)
non-HK/HT	non-hyperkeratotic, non-hypertrophic
RCT	randomized controlled trial
SGB	<i>Sozialgesetzbuch</i> (Social Code Book)

## 2 Benefit assessment

### 2.1 Executive summary of the benefit assessment

#### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ingenol mebutate. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 14.01.2013.

#### Research question

The aim of this benefit assessment was to assess the added benefit of ingenol mebutate gel (150 µg/g) for use on the face and scalp, and of ingenol mebutate gel (500 µg/g) for use on the trunk and extremities in comparison with diclofenac/hyaluronic acid gel (3%) as appropriate comparator therapy (ACT) in adult patients with non-hyperkeratotic, non-hypertrophic (non-HK/HT) actinic keratosis. The assessment was based on patient-relevant outcomes.

The company did not identify any randomized controlled trials (RCTs) with direct comparisons of ingenol mebutate gel and diclofenac/hyaluronic acid gel. It therefore aimed at determining the added benefit on the basis of indirect comparisons. For both ingenol mebutate gel and diclofenac/hyaluronic acid gel, the company identified studies comparing the intervention therapy with a vehicle gel that did not contain ingenol mebutate gel or diclofenac.

The company assumed that the hyaluronic acid gel itself, which served as vehicle in the diclofenac/hyaluronic acid studies, had an effect on actinic keratosis, whereas the drug-free vehicle gel in the ingenol mebutate studies did not. It therefore rejected an adjusted indirect comparison with vehicle gel as intermediate comparator. Instead, it chose a method called "chaining of direct comparisons" for the indirect comparison (comparison of ingenol mebutate gel versus vehicle gel, vehicle gel versus hyaluronic acid gel, and hyaluronic acid gel versus diclofenac/hyaluronic acid gel on the basis of the studies mentioned above). A comparison of ingenol mebutate vehicle and hyaluronic acid gel conducted in RCTs would have been necessary, however, to draw a valid conclusion on added benefit on the basis of the method chosen by the company. The company did not identify such studies. Groups with drug-free vehicle gel from different studies were compared in one step of the method. This was an unadjusted indirect comparison, which rendered randomization ineffective. Unadjusted indirect comparisons do not constitute a valid method of analysis, however.

Moreover, the company included 2 non-randomized comparative studies on ingenol mebutate versus drug-free vehicle gel in the assessment of the outcome "recurrence rate". The company did not identify any studies with diclofenac/hyaluronic acid gel that recorded this outcome.

Hence there were no relevant data for the research question.

## Results

No relevant data were available for the research question of the benefit assessment. Hence the results from RCTs and non-RCTs presented in the dossier were not suitable for assessing the added benefit of ingenol mebutate gel versus diclofenac/hyaluronic acid gel.

### **Extent and probability of added benefit, patient groups with therapeutically important added benefit<sup>3</sup>**

On the basis of the results presented, the extent and probability of the added benefit of the drug ingenol mebutate compared with the ACT is assessed as follows:

No proof of added benefit of ingenol mebutate in comparison with the ACT could be derived from the data presented by the company. Hence there are no patient groups for whom a therapeutically important added benefit could be derived.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

## **2.2 Research question**

The aim of this benefit assessment was to assess the added benefit of ingenol mebutate gel (150 µg/g) for use on the face and scalp, and of ingenol mebutate gel (500 µg/g) for use on the trunk and extremities in adult patients with non-HK/HT actinic keratosis. The company conducted the assessment in comparison with diclofenac/hyaluronic acid gel (3%) as ACT, and thus chose one of the options specified by the G-BA. This approach could be accepted.

The assessment was conducted based on patient-relevant outcomes.

*Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.*

## **2.3 Information retrieval and study pool**

The study pool of the assessment was compiled on the basis of the following information:

- Studies on ingenol mebutate completed by the company up to 17.12.2012 (study list of the company)

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<sup>3</sup> On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

- Results of a search in trial registries for studies on ingenol mebutate (last search on 17.10.2012, searches by the company)
- Results of a search in bibliographical databases and trial registries for studies on the ACT diclofenac/hyaluronic acid gel (last search 15.10.2012 in bibliographical databases, and 17.10.2012 in trial registries, searches by the company). In addition, the company conducted (systematic and unsystematic) searches in bibliographical databases for non-randomized comparative studies. However, this search was inadequate and could therefore not be used (see comment in Section 2.7.2.3.1 of the full dossier assessment).

*Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.*

The company did not identify any RCTs with direct comparisons of ingenol mebutate gel and diclofenac/hyaluronic acid gel. It therefore aimed at determining the added benefit on the basis of indirect comparisons. On the one hand, the company included 5 RCTs that compared ingenol mebutate gel with drug-free vehicle gel. 3 of them refer to use on the face and scalp (studies PEP005-15, PEP005-016 and PEP0025 [3-6]; dosage: 150 µg/g) and 2 to use on the trunk and extremities (PEP005-014 and PEP005-028 [3,7,8]; dosage: 500 µg/g). On the other hand, it included 3 RCTs comparing diclofenac/hyaluronic acid gel (3%) and hyaluronic acid gel (CT1101-03, CT1101-04 and CT1101-07 [9-13]; use both for face/scalp and trunk/extremities).

The company assumed that the hyaluronic acid gel, which served as vehicle in the diclofenac/hyaluronic acid studies, itself had an effect on actinic keratosis, whereas the drug-free vehicle gel in the ingenol mebutate studies did not. It therefore rejected an adjusted indirect comparison according to Bucher [14] with vehicle as intermediate comparator. The method chosen by the company instead included a chaining of direct comparisons, according to the company. This description could not be accepted. The company compared ingenol mebutate gel versus vehicle gel, vehicle gel versus hyaluronic acid gel, and hyaluronic acid gel versus diclofenac/hyaluronic acid gel on the basis of the studies mentioned above. Comparisons were not only conducted between the 2 vehicle gels and the respective intervention groups from RCTs, but also cross-study. Hence the company's "chain" contained an indirect comparison. The isolated comparison of individual study arms from different studies constitutes an unadjusted indirect comparison because it renders randomization ineffective. A randomized direct comparison would require RCTs between the vehicle gel of ingenol mebutate and hyaluronic acid gel. According to the company, no such studies are available, and could not be identified by its search strategy either.

Regarding the outcome "recurrence rate", the company presented results of 2 non-randomized comparative studies [15,16]. These were descriptive presentations of the benefit of ingenol mebutate gel for this outcome based on a follow-up of patients who achieved complete clearance with ingenol mebutate in some of the RCTs mentioned above. No studies with



diclofenac/hyaluronic acid gel were available regarding this outcome. These data were therefore not relevant for the benefit assessment, either.

Hence there were no relevant data for the research question. The Institute therefore dispensed with checking the completeness of the study pool.

*Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 and 4.3.2.2.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.*

## **2.4 Results on added benefit**

No relevant data were available for the research question of the benefit assessment. Hence the results from RCTs and non-RCTs presented in the dossier were not suitable for assessing the added benefit of ingenol mebutate gel versus diclofenac/hyaluronic acid gel. The results are therefore not presented.

*Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3 and 4.3.2.2.3 of the dossier.*

## **2.5 Extent and probability of added benefit**

The data presented in the dossier were not relevant for the research question. Hence there is no proof of added benefit of ingenol mebutate gel versus diclofenac/hyaluronic acid gel. Hence there are no patient groups for whom a therapeutically important added benefit could be derived.

This result deviates from the company's assessment, which derived a considerable added benefit both for the total population of the patients enrolled and for the individual applications on face/scalp and trunk/extremities.

*Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.*

## **2.6 List of included studies**

Not applicable as the company did not present any data in its dossier from which an added benefit of ingenol mebutate gel versus the ACT could be derived.

## **References for English extract**

Please see full dossier assessment for full reference list.

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