IQWiG Reports – Commission No. A18-55

Ingenol mebutate (actinic keratosis) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of the executive summary of the dossier assessment *Ingenolmebutat (aktinische Keratose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ingenol mebutate (actinic keratosis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

3 September 2018

Internal Commission No.:

A18-55

Address of publisher:

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Keywords: ingenol mebutate, keratosis – actinic, benefit assessment, NCT02406014

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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. For the drug to be assessed, the pharmaceutical company (hereinafter referred to as "the company") submitted a dossier for early benefit assessment for the first time on 14 January 2013. The company now requested a new benefit assessment due to new scientific findings.

The assessment is based on a dossier compiled by the company. The dossier was sent to IQWiG on 3 September 2018.

Research question

The aim of this report was to assess the added benefit of ingenol mebutate in comparison with the appropriate comparator therapy (ACT) in patients with non-hyperkeratotic, non-hypertrophic (non-HK/HT) actinic keratosis.

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2[2]: Research questions of the benefit assessment of ingenol mebutate

Indication	**ACT[a]**
Adults with non-hyperkeratotic, non-hypertrophic actinic keratosis	**Diclofenac/hyaluronic acid gel (3%)** or 5-fluorouracil (5-FU) used topically or (surgical) cryotherapy in the treatment of individual lesions
a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. 5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification and selected diclofenac/hyaluronic acid gel (3%) (hereinafter diclofenac/hyaluronic acid gel) from the presented options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 120 days were used to derive any added benefit.

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

Results

Study design

The LP0041-1120 study is a randomized, open-label, multicentre study comparing ingenol mebutate with diclofenac/hyaluronic acid. It included adult patients with 4 to 8 non-HT/HK, clinically typical, visible, and discrete actinic keratosis lesions within a 25 cm² treatment area on the face or scalp. Ingenol mebutate is also approved for the topical treatment of actinic keratosis lesions on the trunk and extremities, but at a higher dosage than for the treatment of actinic keratosis lesions on the face or scalp. The choice of the correct dosage is relevant since the application of higher doses of ingenol mebutate may cause more adverse events, for instance. Since the study did not investigate any patients with actinic keratosis lesions on the trunk or extremities, no conclusions can be drawn on the added benefit of ingenol mebutate for this patient group.

Overall, 502 patients were randomly allocated to the two study arms for treatment with ingenol mebutate (N = 255) or diclofenac/hyaluronic acid (N = 247). The randomization was stratified by study centre and anatomic location of the lesions (face or scalp).

For the study duration of 120 days (17 weeks), the patients in the ingenol mebutate arm each received 1 or 2 treatment cycles by Week 8, depending on their response to treatment, and patients in the diclofenac/hyaluronic acid arm received 1 treatment cycle. Ingenol mebutate was to be applied to the treatment area once daily for 3 consecutive days and diclofenac/hyaluronic acid twice daily for 90 days. For patients in the ingenol mebutate arm who presented without complete clearance of the lesions by Week 8, a 2nd treatment cycle was initiated.

The primary outcome of the study was the complete clearance of visible lesions after 1 treatment cycle, assessed at Week 8 for patients in the ingenol mebutate arm and at Week 17 for patients in the diclofenac/hyaluronic acid arm. Further relevant outcomes were overall mortality and outcomes from the category of morbidity and adverse events.

Risk of bias

For the LP0041-1120 study, the risk of bias at study level is rated as low. The risk of bias for overall mortality and serious adverse events (SAEs) was rated as low. The risk of bias for the outcomes “complete clearance of visible lesions at Week 17” and “reaction at the application site” is rated as high. No usable data are available for the outcomes “squamous cell carcinoma of the skin” and “discontinuation due to adverse events (AEs)”; therefore, the risk of bias was not assessed for these outcomes.

Results

Mortality

In the LP0041-1120 study, no deaths occurred in the ingenol mebutate arm, and 2 deaths occurred in the diclofenac/hyaluronic acid arm. No statistically significant difference between treatment groups was found for the outcome “overall mortality”. Consequently, there is no hint

of an added benefit of ingenol mebutate in comparison with diclofenac/hyaluronic acid; an added benefit is therefore not proven.

Morbidity

Complete clearance of visible lesions by Week 17

As a symptom, complete clearance of visible lesions is a patient-relevant outcome. In both treatment groups, the outcome "complete clearance of visible lesions" is evaluated on the basis of the percentage of patients in whom no lesions were visible by the end of the entire study follow-up at Week 17 (and, for the ingenol mebutate arm, regardless of the received number of treatment courses).

For the outcome "complete clearance of visible lesions", a statistically significant difference in favour of ingenol mebutate was found in comparison with diclofenac/hyaluronic acid at 17 weeks. Consequently, there is a hint of added benefit of ingenol mebutate in comparison with diclofenac/hyaluronic acid.

When interpreting the results for this outcome, it must be noted that 26% of the patients in the ingenol mebutate arm who were lesion-free at Week 8 developed lesions again by Week 17. This shows that permanent or longer-term freedom from lesions is not achieved for a relevant percentage of patients in the ingenol mebutate arm. It remains unclear how many patients experience further recurrences. In the diclofenac/hyaluronic acid arm, no data on recurrences were available at all since the optimal therapeutic effect of diclofenac/hyaluronic acid sometimes does not occur until after 120 days, i.e. at the end of the study, and therefore, no follow-up of recurrences had been planned. The influence of recurrences under diclofenac/hyaluronic acid on the long-term effect regarding the complete clearance of visible lesions as well as the influence of further recurrences under ingenol mebutate can therefore not be judged.

Squamous cell carcinoma of the skin

The question of whether and how treatment with ingenol mebutate in comparison with diclofenac/hyaluronic acid affects the malignant transformation of actinic keratosis lesions (development of squamous cell carcinoma) was not explicitly investigated by the study. The study merely documented cancer-related events at and outside the application site in the context of surveying AEs over the 17-week study duration. However, these data are unusable, first because of the lack of long-term follow-up and, second, due to a lack of data on the localization of the squamous cell carcinomas.

Health-related quality of life

The LP0041-1120 study did not survey any outcomes on health-related quality of life.

Adverse events

SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of ingenol mebutate in comparison with diclofenac/hyaluronic acid; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

The results for the outcome "discontinuation due to AEs" are unusable due to considerable differences in the application durations of ingenol mebutate (3 days) versus diclofenac/hyaluronic acid (90 days). Consequently, there is no hint of greater or lesser harm of ingenol mebutate in comparison with diclofenac/hyaluronic acid; greater or lesser harm is therefore not proven.

Specific AEs

Reaction at the application site

For the outcome "reaction at the application site", no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of ingenol mebutate in comparison with diclofenac/hyaluronic acid; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

Overall, a hint of a positive effect was found for ingenol mebutate in comparison with diclofenac/hyaluronic acid for the outcome "complete clearance of visible lesions by Week 17". The extent of added benefit on the basis of the clearance of visible lesions at Week 17 is assessed as "considerable" because the symptoms are non-serious. However, the study does not allow for any conclusions to be drawn on how lasting this effect will be.

In addition, it remains unclear whether and how the visible clearance of lesions at a certain time point will affect the development of squamous cell carcinoma from actinic keratosis lesions in the long term. No usable data were available on the outcome "squamous cell carcinoma of the skin".

[3] 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 to 3 cannot be drawn from the available data). 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, added benefit not proven, or less benefit). For further details see [1,2].

Overall, for adults with non-HK/HT actinic keratosis lesions on the face and/or scalp, there is a hint of a non-quantifiable – "considerable" at most – added benefit of ingenol mebutate in comparison with diclofenac/hyaluronic acid.

Table 3 presents a summary of the probability and extent of the added benefit of ingenol mebutate.

Table 3: Ingenol mebutate – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with non-hyperkeratotic, non-hypertrophic actinic keratosis	**Diclofenac/hyaluronic acid gel (3%)** or 5-fluorouracil (5-FU) used topically or (surgical) cryotherapy in the treatment of individual lesions	Adults with actinic keratosis lesions on the face and/or scalp: Hint of added benefit; extent: not quantifiable, at most considerable
		Adults with actinic keratosis lesions on the trunk and/or extremities: Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. 5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A19-02) to dossier assessment A18-55 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-55-ingenol-mebutate-actinic-keratosis-benefit-assessment-according-to-35a-social-code-book-v.10488.html.