IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-37

Talimogene laherparepvec (melanoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Talimogen laherparepvec (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 9 September 2016). 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Markus Böhm, University Hospital of Muenster, Germany

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.

IQWiG employees involved in the dossier assessment[2]:

- Raphaela Gorris
- Michaela Florina Kerekes
- Cornelia Rüdig
- Anke Schulz
- Dorothea Sow
- Corinna ten Thoren
- Beate Wieseler
- Min Zhou

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[2] Due to legal data protection regulations, employees have the right not to be named.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BRAF	serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GM-CSF	granulocyte-macrophage colony-stimulating factor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (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 talimogene laherparepvec. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 June 2016.

Research question

The aim of the present report was to assess the added benefit of talimogene laherparepvec in comparison with the appropriate comparator therapy (ACT) in adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

From the G-BA's specification of the ACT, the following 3 research questions resulted for the benefit assessment (Table 2).

Table 2: Research questions of the benefit assessment of talimogene laherparepvec

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment-naive adults with BRAF V600 mutant tumour	Vemurafenib
2	Treatment-naive adults with BRAF V600 wild type tumour	Ipilimumab
3	Pretreated adults	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee

The company named the ACT specified by the G-BA as ACT. It specified several drugs it considered to be an option for individual treatment of pretreated adults for research question 3. However, the company's choice restricted the ACT for pretreated patients. It cannot be excluded that the drugs not mentioned by the company (dacarbazine, lomustine) are also individually suitable for pretreated patients.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

The data presented by the company were unsuitable to draw conclusions on the added benefit of talimogene laherparepvec in comparison with the ACT.

The company identified no studies of direct comparisons that investigated talimogene laherparepvec in comparison with the respective ACT in treatment-naive adults with BRAF V600 mutant tumour (research question 1), or with BRAF V600 wild type tumour (research question 2), or in pretreated adults (research question 3).

The company only identified the approval study of talimogene laherparepvec (study OPTiM). This study compared talimogene laherparepvec with the granulocyte-macrophage colony-stimulating factor (GM-CSF) in adults with unresectable stage IIIb, IIIc and IV malignant melanoma. However, no adequate studies with a comparison with the common comparator GM-CSF for any of the ACTs were available for an indirect comparison. Hence no direct or indirect comparison of talimogene laherparepvec with the ACT was possible for any research question. Nonetheless, the company presented the approval study OPTiM to describe the added benefit of talimogene laherparepvec for all research questions together in the dossier because it considered this study to provide the best available evidence.

The company's approach to use the OPTiM study for all research questions for the benefit assessment was not followed. The comparator of the study, GM-CSF, did not concur with the G-BA's specification of the ACT for treatment-naive patients. Since GM-CSF is not approved for the treatment of melanoma, the drug is also not an option for individual treatment for pretreated patients. The study presented by the company was therefore unsuitable for any research question to investigate the added benefit of talimogene laherparepvec versus the respective ACT.

Hence, no evaluable data were available for the derivation of the added benefit of talimogene laherparepvec in comparison with the ACT.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

[4] 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, no added benefit, or less benefit). For further details see [1,2].

An added benefit of talimogene laherparepvec is not proven because the company presented no suitable data.

Table 3 presents a summary of the extent and probability of the added benefit of talimogene laherparepvec.

Table 3: Talimogene laherparepvec – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy[a]**	**Extent and probability of added benefit**
Treatment-naive adults with BRAF V600 mutant tumour	Vemurafenib	Added benefit not proven
Treatment-naive adults with BRAF V600 wild type tumour	Ipilimumab	Added benefit not proven
Pretreated adults	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of talimogene laherparepvec in comparison with the ACT in adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

From the G-BA's specification of the ACT, the following 3 research questions resulted for the benefit assessment (Table 4).

Table 4: Research questions of the benefit assessment of talimogene laherparepvec

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment-naive adults with BRAF V600 mutant tumour	Vemurafenib
2	Treatment-naive adults with BRAF V600 wild type tumour	Ipilimumab
3	Pretreated adults	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee		

The company named the ACT specified by the G-BA as ACT. It specified several drugs it considered to be an option for individual treatment of pretreated adults for research question 3. However, the company's choice restricted the ACT for pretreated patients. It cannot be excluded that the drugs not mentioned by the company (dacarbazine, lomustine) are also individually suitable for pretreated patients.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Since the company referred its information retrieval to all 3 research questions jointly and presented its study included irrespective of the BRAF mutation status (BRAF: serine/threonine-protein kinase B-Raf [rapidly accelerated fibrosarcoma – isoform B]) and the pretreatment also for all research questions jointly, hereinafter the benefit assessment is also not divided according to the research questions mentioned above.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on talimogene laherparepvec (status: 1 April 2016)

- bibliographical literature search on talimogene laherparepvec (last search on 1 April 2016)
- search in trial registries for studies on talimogene laherparepvec (last search on 1 April 2016)
- bibliographical literature search on the ACT (last search on 1 April 2016)
- search in trial registries for studies on the ACT (last search on 1 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on talimogene laherparepvec (last search on 8 July 2016)
- search in trial registries for studies on the ACT (last search on 8 July 2016)

No additional relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified no studies of direct comparisons that investigated talimogene laherparepvec in comparison with the respective ACT in treatment-naive adults with BRAF V600 mutant tumour (research question 1), or with BRAF V600 wild type tumour (research question 2), or in pretreated adults (research question 3).

The company only identified the approval study of talimogene laherparepvec (study OPTiM [3]). This study compared talimogene laherparepvec with GM-CSF in adults with unresectable stage IIIb, IIIc and IV malignant melanoma. The company stated that no adequate studies for a comparison with the common comparator GM-CSF for any of the ACTs were available. Hence, according to the company, no direct or indirect comparison of talimogene laherparepvec with the ACT was possible for any research question. Nonetheless, the company presented the approval study OPTiM to describe the added benefit of talimogene laherparepvec for all research questions together in the dossier because it considered this study to provide the best available evidence. It justified this as follows:

At the time point of the specification of the study design, besides interleukin 2, only dacarbazine was approved for the treatment of malignant melanoma. The approval of interleukin 2 only referred to the adjuvant administration, which did not concur with the population of the OPTiM study. Since also pretreated patients were to be included in the study, it had to be assumed, according to the company, that these patients had already received dacarbazine and had had recurrence under this treatment. According to the company, dacarbazine was also unsuitable as comparator arm because of this.

Since regular testing of the BRAF V600 mutation status at the time point of patient recruitment to the OPTiM study was not a clinical standard, no complete division of the target population of the study regarding the mutation status, as defined by the G-BA for the

definition of the ACT, could not be conducted. According to the company, talimogene laherparepvec can be used independently from the BRAF V600 mutation status, however.

The company's approach to use the OPTiM study for all research questions for the benefit assessment was not followed. The comparator of the study, GM-CSF, did not concur with the G-BA's specification of the ACT for treatment-naive patients. Since GM-CSF is not approved for the treatment of melanoma, the drug is also not an option for individual treatment for pretreated patients. The study presented by the company was therefore unsuitable for any research question to investigate the added benefit of talimogene laherparepvec versus the respective ACT.

The characteristics of the studies and of the interventions of the OPTiM study are presented in table format in Appendix A of the full dossier assessment.

2.4 Results on added benefit

No data were available for the assessment of the added benefit of talimogene laherparepvec for the treatment of treatment-naive adults with BRAF V600 mutant tumour (research question 1), with BRAF V600 wild type tumour (research question 2) or for pretreated adults (research question 3). Hence there was no hint of an added benefit of talimogene laherparepvec in comparison with the respective ACT. An added benefit is therefore not proven.

2.5 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of talimogene laherparepvec in treatment-naive adults with BRAF V600 mutant tumour (research question 1), with BRAF V600 wild type tumour (research question 2) or for pretreated adults (research question 3), an added benefit is not proven.

The result of the assessment of the added benefit of talimogene laherparepvec in comparison with the ACT is summarized in Table 5.

Table 5: Talimogene laherparepvec – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Treatment-naive adults with BRAF V600 mutant tumour	Vemurafenib	Added benefit not proven
Treatment-naive adults with BRAF V600 wild type tumour	Ipilimumab	Added benefit not proven
Pretreated adults	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee		

This deviates from the company's approach, which derived a non-quantifiable added benefit for the total population of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

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 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.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

3. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol 2015; 33(25): 2780-2788.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-37-talimogene-laherparepvec-benefit-assessment-according-to-35a-social-code-book-v.7494.html.