IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-09

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

Extract

[1] Translation of Assessment module I, Sections I 2.1 to I 2.6, and Assessment module II, Sections II 2.1 to II 2.6, of the dossier assessment *Apremilast – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 2015). 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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Apremilast
Assessment module I
plaque psoriasis

Medical and scientific advice:

No advisor on medical and scientific questions was involved in the present dossier assessment.

IQWiG employees involved in the assessment[1]:

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Keywords: apremilast, psoriasis, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PUVA	psoralen and ultraviolet-A light
SGB	Sozialgesetzbuch (Social Code Book)

I 2 Benefit assessment

I 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 apremilast. 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 16 February 2015.

Research question

The aim of the present report is to assess the added benefit of apremilast in comparison with adalimumab or infliximab or ustekinumab as appropriate comparator therapy (ACT) in adult patients with moderate to severe chronic plaque psoriasis who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Results

The company presented no studies in its dossier that are suitable to compare apremilast in patients with plaque psoriasis with the ACT. Hence an added benefit of apremilast in comparison with the ACT (adalimumab or infliximab or ustekinumab) is not proven for patients with plaque psoriasis.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

Since no relevant studies were presented for the assessment of the added benefit of apremilast in patients with plaque psoriasis, an added benefit versus the ACT specified by the G-BA (adalimumab or infliximab or ustekinumab) is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 1 presents a summary of the extent and probability of the added benefit of apremilast in the therapeutic indication plaque psoriasis.

[2] 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), 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].

Table 1: Apremilast – extent and probability of added benefit in the therapeutic indication plaque psoriasis

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA	**Adalimumab** or **infliximab** or **ustekinumab**	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PUVA: psoralen and ultraviolet-A light		

This result concurs with the company's assessment, which also derived no added benefit of apremilast in plaque psoriasis. The G-BA decides on the added benefit.

I 2.2 Research question

The aim of the present report is to assess the added benefit of apremilast in comparison with adalimumab or infliximab or ustekinumab as ACT in adult patients with moderate to severe chronic plaque psoriasis who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

In its dossier, the company followed the G-BA's specification of the ACT (adalimumab or infliximab or ustekinumab). It did not limit its conclusions on the added benefit to one of the ACT options.

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

I 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 apremilast (studies completed up to 5 February 2015)
- bibliographical literature search on apremilast (last search on 13 January 2015)
- search in trial registries for studies on apremilast (last search on 13 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on apremilast (last search on 31 March 2015)

No additional relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified only placebo-controlled studies [3-10] and one 3-arm study [11], in which apremilast was compared with placebo and etanercept. There were no studies with plaque psoriasis patients in which apremilast was directly compared with one of the drugs of the ACT. It is therefore not possible to assess the added benefit of apremilast on the basis of studies of direct comparisons.

When no studies of direct comparisons are available, it is possible to investigate the added benefit on the basis of indirect comparisons. The company described in its dossier that it had decided against investigating the added benefit of apremilast with indirect comparisons. Correspondingly, it did not search for studies with the ACT, which might be suitable for an indirect comparison with apremilast. Hence it remains unclear whether an indirect comparison would have been possible. The company also presented no further documents (non-randomized comparative studies or further investigations) to investigate the added benefit of apremilast.

In summary, the company presented no studies in its dossier that are suitable to investigate the added benefit of apremilast in plaque psoriasis in comparison with the ACT.

I 2.4 Results on added benefit

The company presented no studies in its dossier that are suitable to compare apremilast in patients with plaque psoriasis with the ACT. Hence an added benefit of apremilast in comparison with the ACT (adalimumab or infliximab or ustekinumab) is not proven for patients with plaque psoriasis.

I 2.5 Extent and probability of added benefit

Since no relevant studies for the assessment of the added benefit of apremilast in patients with plaque psoriasis were presented, the added benefit versus the ACT specified by the G-BA (adalimumab or infliximab or ustekinumab) is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The result of the assessment of the added benefit of apremilast in comparison with the ACT is summarized in Table 2.

Table 2: Apremilast – extent and probability of added benefit in the therapeutic indication plaque psoriasis

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).	**Adalimumab** or **infliximab** or **ustekinumab**	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PUVA: psoralen and ultraviolet-A light.		

This result concurs with the company's assessment, which also derived no added benefit of apremilast in plaque psoriasis. The company described that it considered the added benefit based on controlled comparative studies to be unprovable because there were no studies of direct comparisons.

The G-BA decides on the added benefit.

I 2.6 List of included studies

Not applicable as the company did not present any relevant studies in the dossier, on the basis of which an added benefit of apremilast versus the ACT specified by the G-BA can be investigated.

References for English extract

Please see full assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 4.2. Köln: IQWiG; 2015. URL: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

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6. Celgene. Study to evaluate safety and effectiveness of oral apremilast (CC-10004) in patients with moderate to severe plaque psoriasis (ESTEEM 1): full text view [online]. In: ClinicalTrials.gov. 29 January 2015 [accessed: 22 April 2015]. URL: http://clinicaltrials.gov/show/NCT01194219.

7. Celgene. Study to evaluate safety and effectiveness of oral apremilast (CC-10004) in patients with moderate to severe plaque psoriasis (ESTEEM 1): study results [online]. In: ClinicalTrials.gov. 29 January 2015 [accessed: 22 April 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01194219.

8. Celgene. Study to evaluate safety and effectiveness of oral apremilast (CC-10004) in patients with moderate to severe plaque psoriasis: (ESTEEM 2); full text view [online]. In: ClinicalTrials.gov. 29 January 201 [accessed: 22 April 2015]. URL: https://clinicaltrials.gov/show/NCT01232283.

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11. Celgene. Phase 3b safety and efficacy study of apremilast to treat moderate to severe plaque-plaque psoriasis: full text view [online]. In: ClinicalTrials.gov. 24 February 2015 [accessed: 22 April 2015]. URL: https://clinicaltrials.gov/show/NCT01690299.

Apremilast
Assessment module II
psoriatic arthritis

Medical and scientific advice:

No advisor on medical and scientific questions was involved in the present dossier assessment.

IQWiG employees involved in the assessment[1]:

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- Thomas Kaiser
- Cornelia Rüdig
- Siw Waffenschmidt

Keywords: apremilast, arthritis – psoriatic, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DMARD	disease-modifying antirheumatic drug
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)
TNFα	tumour necrosis factor alpha

II 2 Benefit assessment

II 2.2 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 apremilast. 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 16 February 2015.

Research question

The aim of the present report is to assess the added benefit of apremilast (alone or in combination with disease-modifying antirheumatic drugs [DMARDs]) in comparison with a tumour necrosis factor alpha (TNFα) inhibitor (etanercept or adalimumab or infliximab or golimumab), if applicable in combination with methotrexate, as appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis who have not responded well enough to or have not tolerated previous DMARD therapy.

Results

The company presented no studies in its dossier that are suitable to compare apremilast with the ACT in patients with psoriatic arthritis. Hence an added benefit of apremilast in comparison with the ACT (TNFα inhibitor [etanercept or adalimumab or infliximab or golimumab], if applicable in combination with methotrexate) is not proven for patients with psoriatic arthritis.

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

Since no relevant study was presented for the assessment of the added benefit of apremilast in patients with psoriatic arthritis, an added benefit versus the ACT specified by the G-BA (TNFα inhibitor [etanercept or adalimumab or infliximab or golimumab], if applicable in combination with methotrexate) is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 1 presents a summary of the extent and probability of the added benefit of apremilast in the therapeutic indication psoriatic arthritis.

Table 1: Apremilast – extent and probability of added benefit in the therapeutic indication psoriatic arthritis

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment (alone or in combination with DMARDs) of active psoriatic arthritis in adult patients who have not responded well enough to or have not tolerated previous DMARD therapy	TNFα inhibitor (**etanercept** or **adalimumab** or **infliximab** or **golimumab**), **if applicable in combination with methotrexate**	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee		

This result concurs with the company's assessment, which also derived no added benefit of apremilast in psoriatic arthritis. The G-BA decides on the added benefit.

II 2.3 Research question

The aim of the present report is to assess the added benefit of apremilast (alone or in combination with DMARDs) in comparison with a TNFα inhibitor (etanercept or adalimumab or infliximab or golimumab), if applicable in combination with methotrexate, as ACT in adult patients with active psoriatic arthritis who have not responded well enough to or have not tolerated previous DMARD therapy.

In its dossier, the company followed the G-BA's specification of the ACT. It did not limit its conclusions on the added benefit to one of the ACT options.

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

II 2.4 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 apremilast (studies completed up to 5 February 2015)
- bibliographical literature search on apremilast (last search on 13 January 2015)
- search in trial registries for studies on apremilast (last search on 13 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on apremilast (last search on 31 March 2015)

No additional relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified only placebo-controlled studies [1-11]. There were no studies with psoriatic arthritis patients in which apremilast was directly compared with one of the drugs of the ACT. It is therefore not possible to assess the added benefit of apremilast on the basis of studies of direct comparisons.

When no studies of direct comparisons are available, it is possible to investigate the added benefit on the basis of indirect comparisons. The company described in its dossier that it had decided against investigating the added benefit of apremilast with indirect comparisons. Correspondingly, it did not search for studies with the ACT, which might be suitable for an indirect comparison with apremilast. Hence it remains unclear whether an indirect comparison would have been possible. The company also presented no further documents (non-randomized comparative studies or further investigations) to investigate the added benefit of apremilast.

In summary, the company presented no studies in its dossier that are suitable to investigate the added benefit of apremilast in psoriatic arthritis in comparison with the ACT.

II 2.5 Results on added benefit

The company presented no studies in its dossier that are suitable to compare apremilast with the ACT in patients with psoriatic arthritis. Hence an added benefit of apremilast (alone or in combination with DMARDs) in comparison with the ACT (TNFα inhibitor [etanercept or adalimumab or infliximab or golimumab], if applicable in combination with methotrexate) is not proven for patients with psoriatic arthritis.

II 2.6 Extent and probability of added benefit

Since no relevant study was presented for the assessment of the added benefit of apremilast (alone or in combination with DMARDs) in patients with psoriatic arthritis, an added benefit versus the ACT specified by the G-BA (TNFα inhibitor [etanercept or adalimumab or infliximab or golimumab], if applicable in combination with methotrexate) is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The result of the assessment of the added benefit of apremilast in comparison with the ACT is summarized in Table 2.

Table 2: Apremilast – extent and probability of added benefit in the therapeutic indication psoriatic arthritis

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment (alone or in combination with DMARDs) of active psoriatic arthritis in adult patients who have not responded well enough to or have not tolerated previous DMARD therapy	TNFα inhibitor (**etanercept** or **adalimumab** or **infliximab** or **golimumab**), **if applicable in combination with methotrexate**	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee		

This result concurs with the company's assessment, which also derived no added benefit of apremilast in psoriatic arthritis. The company described that it considered the added benefit based on controlled comparative studies to be unprovable because there were no studies of direct comparisons.

The G-BA decides on the added benefit.

II 2.7 List of included studies

Not applicable as the company did not present any relevant studies in the dossier, on the basis of which an added benefit of apremilast versus the ACT specified by the G-BA can be investigated.

References for English extract

Please see full assessment for full reference list.

1. Celgene. Phase II study with CC-10004 in psoriatic arthritis: full text view [online]. In: ClinicalTrials.gov. 22 November 2013 [accessed: 13 January 2015]. URL: https://clinicaltrials.gov/show/NCT00456092.

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