IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-48

Fingolimod (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Fingolimod (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 February 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Fingolimod (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

23 November 2015

Internal Commission No.:

A15-48

Address of publisher:

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Keywords: fingolimod, multiple sclerosis – relapsing-remitting, benefit assessment

[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
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN-β	interferon beta
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mFIS	Modified Fatigue Impact Scale
MSFC	Multiple Sclerosis Functional Composite
PRIMUS	Patient-Reported Indices for Multiple Sclerosis
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
QoL	quality of life
SGB	Sozialgesetzbuch (Social Code Book)
TI	therapeutic indication
VAS	visual analogue scale

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 fingolimod (new therapeutic indication). 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 23 November 2015.

Research question

The aim of this report was to assess the added benefit of fingolimod in comparison with the appropriate comparator therapy (ACT) for the change to the therapeutic indication of fingolimod from October 2015.

The assessment refers to adult patients with relapsing remitting multiple sclerosis (RRMS) with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy. The diagnostic criteria for high disease activity previously defined were eliminated in the new therapeutic indication. At the same time, the duration of the prior therapy is no longer limited to at least one year in the new therapeutic indication. According to the G-BA, the new therapeutic indication was to be considered in its entirety because of the complex delimitation of the patient population of the newly formulated therapeutic indication from the patient population comprised by the prior therapeutic indication.

Due to the change in the therapeutic indication, patients who have not yet received a full and adequate course of treatment with at least one disease-modifying therapy are no longer included in the therapeutic indication and were therefore not subject of this assessment.

Patients with rapidly evolving severe RRMS were also not subject of the present assessment because this patient population was not affected by the change in the therapeutic indication.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA for the research question presented in Table 2.

Table 2: Therapeutic indications and ACTs for fingolimod

Research question	Therapeutic indication	ACT specified by the G-BA
A	Patients with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy	Glatiramer acetate or IFN-β1a or 1b, switching depended on prior therapy
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis		

Results

The study CFTY720D2302 (hereinafter referred to as "TRANSFORMS") was included in the assessment. The company assessed a subpopulation of the TRANSFORMS study for the present benefit assessment. This subpopulation was identical to the subpopulation already presented in the dossier from 2 June 2014. These were patients with highly active RRMS who had received full previous treatment with a disease-modifying therapy other than interferon beta (IFN-β). The subpopulation was already assessed in dossier assessment A14-21. Even though the therapeutic indication regarding the criteria "duration of pretreatment" and "definition of a highly active disease" has changed in comparison with 2014, this subpopulation of the TRANSFORMS study is also suitable for the assessment of the changed therapeutic indication because it constitutes an adequate approximation of the population comprised by the therapeutic indication. No relevant deviations in comparison with dossier assessment A14-21 resulted from the newly submitted dossier: There was no hint of an added benefit or greater harm of fingolimod in comparison with the ACT for any of the relevant outcomes.

No study of direct comparison was identified for patients pretreated with IFN-β. Hence no data were available for this patient population.

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 fingolimod compared with the ACT is assessed as follows:

Since neither positive nor negative effects were shown, an added benefit of fingolimod in comparison with the ACT is not proven for patients with highly active RRMS who have not responded to a full and adequate course of treatment with a disease-modifying therapy other than IFN-β, in this case glatiramer acetate.

No data were available for patients with highly active RRMS who have not responded to a full and adequate course of IFN-β. The added benefit for this patient population is therefore not proven.

Also no data were available for patients who have received a disease-modifying therapy other than glatiramer acetate or IFN-β before treatment with fingolimod. The added benefit is also not proven here.

[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].

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

Table 3: Fingolimod – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
A	Patients with highly active RRMS who have not responded to a full and adequate course of treatment with at least one disease-modifying therapy	Glatiramer acetate or IFN-β1a or 1b, switching depended on prior therapy	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis			

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of fingolimod in comparison with the ACT for the change to the therapeutic indication of fingolimod from October 2015.

The assessment refers to adult patients with RRMS with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy. The diagnostic criteria for high disease activity previously defined were eliminated in the new therapeutic indication. At the same time, the duration of the prior therapy is no longer limited to at least one year in the new therapeutic indication. According to the G-BA, the new therapeutic indication was to be considered in its entirety because of the complex delimitation of the patient population of the newly formulated therapeutic indication from the patient population comprised by the prior therapeutic indication.

Due to the change in the therapeutic indication, patients who have not yet received a full and adequate course of treatment with at least one disease-modifying therapy are no longer included in the therapeutic indication [3] and were therefore not subject of this assessment (see also Section 1.2 of the full dossier assessment).

Patients with rapidly evolving severe RRMS were also not subject of the present assessment because this patient population was not affected by the change in the therapeutic indication.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA for the research question presented in Table 4.

Table 4: Therapeutic indications and ACTs for fingolimod

Research question	Therapeutic indication	ACT specified by the G-BA
A	Patients with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy	Glatiramer acetate or IFN-β1a or 1b, switching depended on prior therapy
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis		

The company followed the G-BA with regard to the ACT. The company divided the population of research question A according to the type of pretreatment into patients previously treated with IFN-β and patients previously treated with a disease-modifying therapy other than IFN-β. The company derived glatiramer acetate as ACT for the first group, and IFN-β1a or 1b for the second group.

In research question B, the company additionally considered patients who have not yet received sufficient disease-modifying therapy. The new therapeutic indication does not comprise this patient population, however, so that this research question is not subject of the present assessment (see Section 1.2 of the full dossier assessment).

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 12 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 fingolimod (status: 30 September 2015)
- bibliographical literature search on fingolimod (last search on 16 October 2015)
- search in trial registries for studies on fingolimod (last search on 15 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 7 December 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study CFTY720D2302 (hereinafter referred to as "TRANSFORMS") listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: fingolimod vs. IFN-β1a

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CFTY720D2302 (TRANSFORMS)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. IFN-β: interferon beta; RCT: randomized controlled trial; vs.: versus			

The study of direct comparison TRANSFORMS was identified for patients pretreated with a disease-modifying therapy other than IFN-β. The company assessed a subpopulation of the TRANSFORMS study for the present benefit assessment. This subpopulation was identical to the subpopulation already presented in the dossier from 2 June 2014. These were patients with highly active RRMS who had received full previous treatment with a disease-modifying therapy other than IFN-β. The subpopulation was already assessed in dossier assessment A14-21 [4]. Even though the therapeutic indication regarding the criteria "duration of pretreatment" and "definition of a highly active disease" has changed in comparison with 2014, this subpopulation of the TRANSFORMS study is also suitable for the assessment of the changed therapeutic indication because it constitutes an adequate approximation of the population comprised by the therapeutic indication. Hence hereinafter, as far as possible, benefit assessment A14-21 [4] is referred to for the population of patients pretreated with a disease-modifying therapy other than IFN-β. Deviations in the company's dossier from 20 November 2015 in comparison with the dossier from 2 June 2014 are described in the present benefit assessment. The tables of benefit assessment A14-21 are additionally presented in Appendix A of the full version of the present dossier assessment. Individual adjustments were made based on information in the dossier from 20 November 2015, all of which had no effects on the result of the present benefit assessment, however.

No study of direct comparison was identified for patients pretreated with IFN-β. No data were available for this patient population. The following sections therefore only refer to the population of patients previously treated with a disease-modifying therapy other than IFN-β.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Study characteristics

Table 11 and Table 12 in Appendix A of the full dossier assessment describe the study included for the benefit assessment. A detailed explanation of these tables can be found in dossier assessment A14-21 [4].

The characteristics of the relevant subpopulation of the TRANSFORMS study are presented in Table 13 in Appendix A of the full dossier assessment; the risk of bias at study level is presented in Table 14 in Appendix A of the full dossier assessment.

Relevant patient population

The company's dossier contained the analysis of a subpopulation of the TRANSFORMS study for patients with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy who had received previous treatment with a disease-modifying therapy other than IFN-β. For this purpose, the company analysed those patients who had received glatiramer acetate as the last treatment before the start of the study.

Due to the changed therapeutic indication, the following additional aspects are particularly relevant for the present assessment in comparison with the previous assessments of fingolimod:

- operationalization of a full and adequate course of pretreatment
- diagnostic criteria of the highly active RRMS

The subpopulation of the TRANSFORMS study presented by the company adequately represented the patient population relevant for the present research question (limited to patients pretreated with glatiramer acetate).

2.4 Results on added benefit

The tables of the results on the added benefit are presented in Appendix A of the full dossier assessment (Table 15 to Table 20).

2.4.1 Outcomes included

The patient-relevant outcomes cited in benefit assessment A14-21 were included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment and benefit assessment A14-21 [4]).

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A) (see Section 2.7.2.4.3 of the full dossier assessment and benefit assessment A14-21 [4]).

Table 15 in Appendix A of the full dossier assessment shows for which outcomes data were available in the studies included.

2.4.2 Risk of bias

Table 16 in Appendix A of the full dossier assessment shows the risk of bias for the relevant outcomes.

An assessment of the risk of bias at outcome level can be found in benefit assessment A14-21 [4].

Since the proportion of the patients not considered in the analysis differed by > 15 percentage points between the arms, there were no evaluable data for the following outcomes: disability severity (Multiple Sclerosis Functional Composite, MSFC-z), fatigue (Modified Fatigue Impact Scale, mFIS), activities of daily living (Patient-Reported Indices for Multiple Sclerosis [PRIMUS] Activities), health status (European Quality of Life-5 Dimensions visual analogue scale, EQ-5D VAS) and health-related quality of life (PRIMUS quality of life, QoL). This does not concur with the assessment of the company, which assessed the risk of bias high due to the proportions of – differentially - missing values and analysed the results of the questionnaires.

2.4.3 Results

Table 17 to Table 20 as well as Figure 1 and Figure 2 in Appendix A of the full dossier assessment summarize the results on the comparison of fingolimod with IFN-β1a in patients with highly active RRMS despite full and adequate pretreatment with a disease-modifying therapy other than IFN-β (in this case glatiramer acetate). Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. As supplementation to the data of benefit assessment A14-21, the most common adverse events of the relevant patient population are presented in Table 20 of the full dossier assessment.

The results of the individual outcomes are described and interpreted in Section 2.4.1.3 of benefit assessment A14-21 [4].

2.4.4 Subgroups and other effect modifiers

The available data on subgroups and other effect modifiers could not be meaningfully interpreted (for reasons, see Section 2.7.2.4.3 of the full dossier assessment and benefit assessment A14-21 [4]).

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The extent of added benefit at outcome level was estimated from the results presented in Table 17 to Table 20 and Figure 1 and Figure 2 in Appendix A of the full dossier assessment (see Table 6).

Table 6: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a

Outcome category **Outcome**	**Fingolimod vs. IFN-β1a** **Median of time to event or proportion of events** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**
Mortality		
Deaths	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Relapse-related outcomes (based on EDSS)		
Time to first confirmed relapse	NA vs. NA HR 1.82 [0.67; 4.92] 0.237	Added benefit not proven
Proportion of patients with confirmed relapse	47.1% vs. 32.0% RR 1.47 [0.69; 3.15] 0.359[b]	Added benefit not proven
Annualized relapse rate	0.67 vs. 0.51 rate ratio 1.32 [0.56; 3.10] 0.530	Added benefit not proven
Disability progression (based on EDSS)		
Time to first confirmed disability progression at month 12	NA vs. NA ND[c] > 0.999	Added benefit not proven
Proportion of patients with confirmed disability progression at month 12	5.9% vs. 4.0% RR 1.47 [0.10; 21.94] 0.807[b]	Added benefit not proven
Disability severity (MSFC)	No evaluable data available	Added benefit not proven
Fatigue (using MFIS)	No evaluable data available	Added benefit not proven
Activities of daily living (using PRIMUS activities)	No evaluable data available	Added benefit not proven
Health status (EQ-5D VAS)	No evaluable data available	Added benefit not proven
Health-related quality of life		
PRIMUS QoL	No evaluable data available	Added benefit not proven
Adverse events		
Serious adverse events	5.9% vs. 4.0% RR 1.47 [0.10; 21.94] 0.780	Lesser/greater harm not proven
Discontinuation due to adverse events	11.8% vs. 0.0% RR 7.22 [0.37; 141.67] 0.193	Lesser/greater harm not proven

(continued)

Table 6: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (continued)

a: Probability provided if statistically significant differences are present. b: Institute's calculation, unconditional exact test (CSZ method according to [5]). c: According to the information provided by the company, this value cannot be estimated because "no adjustment of the model is possible". CI: confidence interval; CSZ: convexity, symmetry, z score; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IFN-β: interferon beta; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; NA: not achieved; ND: no data; PRIMUS: Patient-Reported Indices for Multiple Sclerosis, QoL: quality of life; RR: relative risk; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Since neither positive nor negative effects were shown, an added benefit of fingolimod in comparison with the ACT is not proven for patients with highly active RRMS who have not responded to a full and adequate course of treatment with a disease-modifying therapy other than IFN-β, in this case glatiramer acetate.

No data were available for patients with highly active RRMS who have not responded to a full and adequate course of IFN-β. The added benefit for this patient population is therefore not proven.

Also no data were available for patients who have received a disease-modifying therapy other than glatiramer acetate or IFN-β before treatment with fingolimod. The added benefit is also not proven here.

In summary, the added benefit of fingolimod compared with the ACT is not proven for patients with highly active RRMS despite a full and adequate pretreatment with a disease-modifying therapy.

The result of the assessment of the added benefit of fingolimod in comparison with the ACT is summarized in Table 7.

Table 7: Fingolimod – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
A	Patients with highly active RRMS who have not responded to a full and adequate course of treatment with at least one disease-modifying therapy	Glatiramer acetate or IFN-β1a or 1b, switching depended on prior therapy	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis			

This concurs with the company's approach, which also derived no added benefit for patients with highly active RRMS despite full and adequate pretreatment with a disease-modifying therapy (IFN-β or other than IFN-β).

The G-BA decides on the added benefit.

2.6 List of included studies

TRANSFORMS

Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. CNS Neurosci Ther 2014; 20(5): 446-451.

Chinea Martinez AR, Correale J, Coyle PK, Meng X, Tenenbaum N. Efficacy and safety of fingolimod in Hispanic patients with multiple sclerosis: pooled clinical trial analyses. Adv Ther 2014; 31(10): 1072-1081.

Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 402-415.

Cohen JA, Barkhof F, Comi G, Izquierdo G, Khatri B, Montalban X et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol 2013; 260(8): 2023-2032.

DiMarco JP, O'Connor P, Cohen JA, Reder AT, Zhang-Auberson L, Tang D et al. First-dose effects of fingolimod: pooled safety data from three phase 3 studies. Mult Scler Relat Disord 2014; 3(5): 629-638.

Kappos L, Cohen J, Collins W, De Vera A, Zhang-Auberson L, Ritter S et al. Fingolimod in relapsing multiple sclerosis: an integrated analysis of safety findings. Mult Scler Relat Disord 2014; 3(4): 494-504.

Khatri B, Barkhof F, Comi G, Hartung HP, Kappos L, Montalban X et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol 2011; 10(6): 520-529.

Khatri BO, Pelletier J, Kappos L, Hartung HP, Comi G, Barkhof F et al. Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. interferon beta-1a intramuscular: subgroup analyses of the trial assessing injectable interferon vs. Fingolimod oral in relapsing-remitting multiple sclerosis (TRANSFORMS). Mult Scler Relat Disord 2014; 3(3): 355-363.

Meng X, Chin PS, Hashmonay R, Zahur Islam M, Cutter G. Effect of switching from intramuscular interferon beta-1a to oral fingolimod on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. Contemp Clin Trials 2015; 41: 69-74.

Novartis. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis with optional extension phase (TRANSFORMS): study results [online]. In: ClinicalTrials.gov. 14 January 2014 [accessed: 5 January 2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00340834.

Novartis. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis with optional extension phase (TRANSFORMS): full text view [online]. In: ClinicalTrials.gov. 14 January 2014 [accessed: 5 January 2016]. URL: https://ClinicalTrials.gov/show/NCT00340834.

Novartis. A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon ß-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional extension phase: study no CFTY720D2302; full clinical study report [unpublished]. 2008.

Novartis. A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon ß-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional extension phase: study CFTY720D2302; Zusatzanalysen [unpublished]. 2015.

Novartis Pharma Services. A 12-month double-blind, randomized, multicenter, active controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional Extension Phase [online]. In: EU Clinical Trials Register. [Accessed: 5 January 2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-000704-17.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-48-fingolimod-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v.7151.html.