IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Fingolimod

(Addendum to Commission A14-21)[1]

Addendum

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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Thomas Kaiser
- Charlotte Guddat
- Michaela Florina Kerekes

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

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Abbreviation	Meaning
AE	adverse event
FIS	Fatigue Impact Scale
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 (interim version for the validation of the U-FIS)
MFIS	Modified Fatigue Impact Scale (validated abbreviated version of the FIS)
PT	Preferred Term
RR	relative risk
RRMS	relapsing remitting multiple sclerosis
SOC	System Organ Class
U-FIS	Unidimensional Fatigue Impact Scale

1 Background

On 12 November 2014 (supplemented on 18 November 2014), the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-21 (benefit assessment of fingolimod [1]).

In the commenting procedure on the assessment of fingolimod, the pharmaceutical company (hereinafter abbreviated to "the company") submitted supplementary information for the proof of added benefit to the G-BA [2,3] that went beyond the information in the dossier [4]. These were analyses on adverse events (AEs) and information on the Fatigue Impact Scale (FIS).

The G-BA commissioned IQWiG with the assessment of the supplementary information on AEs and on the FIS submitted by the company.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Supplementary information on adverse events

It was criticised in dossier assessment A14-21 [1] that the company in its dossier presented no complete data on specific AEs from the TRANSFORMS study for the relevant subpopulation 1 (patients with highly active relapsing remitting multiple sclerosis [RRMS], full previous treatment with disease-modifying therapy [other than interferon beta, IFN-β]) [4]. The company supplemented these data with the comments.

The following Table 1 shows the corresponding results. Due to the small size of the relevant subpopulation (42 patients in total, of which 17 fingolimod patients and 25 IFN-β patients), only those AEs are presented that occurred in at least 10% of the patients of one group. This is equivalent to at least 2 patients in the fingolimod arm and at least 3 patients in the IFN-β arm.

Due to the small size of the relevant subpopulation, p-values were calculated for an unconditional exact test (CSZ method according to [5], Institute's calculation). Relative risks (RRs) and corresponding 95% confidence intervals are only presented in cases where the test result is statistically significant. Discrepancies between p-value (exact) and confidence interval (asymptotic) can occur because of different calculation methods. The result of the p-value from the unconditional exact test was decisive for the decision regarding statistical significance.

Table 1: Results on AEs (≥ 10% in at least one study arm) – RCT, direct comparison: fingolimod vs. IFN-β

Study SOC PT	Fingolimod		IFN-β		Fingolimod vs. IFN-β
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]; p-value[b]
Study TRANSFORMS					
Adverse events					
Infections and infestations	17	11 (64.7)	25	9 (36.0)	ND 0.071
Nasopharyngitis	17	5 (29.4)	25	4 (16.0)	ND 0.334
Rhinitis	17	3 (17.6)	25	2 (8.0)	ND 0.454
Urinary tract infection	17	2 (11.8)	25	0 (0.0)	ND 0.094
Nervous system disorders	17	10 (58.8)	25	6 (24.0)	2.45 [1.10; 5.47] 0.024
Headache	17	4 (23.5)	25	4 (16.0)	ND 0.602
Dizziness	17	2 (11.8)	25	0 (0)	ND 0.094
Paresthesia	17	2 (11.8)	25	0 (0)	ND 0.094
Investigations	17	6 (35.3)	25	0 (0)	18.78 [1.13; 312.8][c] 0.001
Alanine aminotransferase increased	17	2 (11.8)	25	0 (0)	ND 0.094
Hepatic enzyme increased	17	2 (11.8)	25	0 (0)	ND 0.094
Musculoskeletal and connective tissue disorders	17	6 (35.3)	25	8 (32.0)	ND 0.909
Back pain	17	5 (29.4)	25	1 (4.0)	7.35 [0.94; 57.50][d] 0.023
Myalgia	17	1 (5.9)	25	4 (16.0)	ND 0.334
Arthralgia	17	0 (0)	25	3 (12.0)	ND 0.155
Psychiatric disorders	17	5 (29.4)	25	5 (20.0)	ND 0.566
Depression	17	3 (17.6)	25	3 (12.0)	ND 0.617
Sleep disorder	17	2 (11.8)	25	0 (0)	ND 0.094

(continued)

Table 1: Results on AEs (≥ 10% in at least one study arm) – RCT, direct comparison: fingolimod vs. IFN-β (continued)

Study SOC PT	Fingolimod		IFN-β		Fingolimod vs. IFN-β
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]; p-value[b]
Skin and subcutaneous tissue disorders	17	4 (23.5)	25	4 (16.0)	ND 0.602
Alopecia	17	2 (11.8)	25	0 (0)	ND 0.094
Eye disorders	17	3 (17.6)	25	2 (8.0)	ND 0.454
Gastrointestinal disorders	17	3 (17.6)	25	7 (28.0)	ND 0.566
Nausea	17	1 (5.9)	25	3 (12.0)	ND 0.567
Neoplasms benign, malignant and unspecified (including cysts and polyps)	17	3 (17.6)	25	1 (4.0)	ND 0.180
Cutaneous neoplasms benign	17	2 (11.8)	25	1 (4.0)	ND 0.422
Renal and urinary disorders	17	3 (17.6)	25	1 (4.0)	ND 0.180
Pollakisuria	17	2 (11.8)	25	0 (0)	ND 0.094
General disorders and administration site conditions	17	2 (11.8)	25	19 (76.0)	0.15 [0.04; 0.58] < 0.001
Influenza like illness	17	1 (5.9)	25	9 (36.0)	0.16 [0.02; 1.17][d] 0.026
Fatigue	17	0 (0)	25	3 (12.0)	ND 0.155
Injury, poisoning and procedural complications	17	2 (11.8)	25	2 (8.0)	ND 0.708
Reproductive system and breast disorders	17	2 (11.8)	25	1 (4.0)	ND 0.422
Respiratory, thoracic and mediastinal disorders	17	2 (11.8)	25	3 (12.0)	ND > 0.999

a: RR and CI are only presented if the effect is statistically significant according to the unconditional exact test (CSZ method according to [5]).
b: Institute's calculation, unconditional exact test (CSZ method according to [5]).
c: The company determined RR and CI using a correction term of 0.5, which was added to each cell frequency.
d: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

CI: confidence interval; CSZ: convexity, symmetry, z score; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with event; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; vs.: versus

The results showed a statistically significant result to the disadvantage of fingolimod for the AEs "nervous system disorders (System Organ Class, SOC)", "investigations (SOC)", and "back pain (Preferred Term, PT)". The patient relevance of the result on the SOC "investigations" is questionable because the difference was primarily based on changes in laboratory values. In contrast, there was a statistically significant result in favour of fingolimod for the SOC "general disorders and administration site conditions". The result was apparently mainly caused by the event "influenza like illness (PT)".

The results were imprecise because of the small sample size. It does not appear meaningful to conduct a derivation on the extent of added benefit on the AEs "nervous system disorders", "back pain" and "influenza like illness" on the basis of the confidence intervals in the present specific data situation[3], particularly because the confidence intervals of the AEs "back pain" and "influenza like illness" include the relative risk of 1.

Overall, the data on AEs showed no clear advantage or disadvantage of fingolimod versus IFN-β. Under consideration of the results from dossier assessment A14-21, including regarding the outcomes "relapses" and "disability progression", there is therefore still no proof of an added benefit of fingolimod versus IFN-β in subpopulation 1 (patients with highly active RRMS, full previous treatment with disease-modifying therapy [other than IFN-β]).

2.2 Supplementary information on the recording of fatigue

It was noted in dossier assessment A14-21 [1] that it remained unclear in the company's dossier [4] which questionnaire was used in the TRANSFORMS study for recording fatigue. Background for this was, among other things, the inconsistent use of the terms "Modified FIS (mFIS)" and "Unidimensional FIS (U-FIS)" in the dossier. Furthermore, the company stated that it had used the mFIS questionnaire comprising 39 questions, but referred to the publications Elbers 2011 and Kos 2005 on MFIS, an abbreviated version of FIS comprising 21 questions [6,7]. The company could not resolve this discrepancy in the hearing on the dossier assessment A14-21 [8].

Subsequent to the hearing, the company submitted supplementary information on the recording of fatigue in the TRANSFORMS study [3]. This information showed that the questionnaire used in the TRANSFORMS study was not the validated MFIS questionnaire, which comprises 21 questions, but an unvalidated questionnaire, which comprises 39 questions, and which only constituted an interim version on the way to the validation of the U-FIS. The company called this questionnaire "mFIS". This is referred to as „draft 39-item version of the U-FIS" in the corresponding validation publication of the U-FIS [9].

The analysis of the data recorded with the mFIS was conducted in the company's dossier as if they had been recorded with the questionnaire for the U-FIS. However, mFIS and U-FIS differ considerably from each other: On the one hand, mFIS comprises 39 questions, whereas

[3] This approach corresponds to the one in dossier assessment A11-23 on fingolimod in a similar data situation.

U-FIS comprises 22 questions (a subset of the 39 mFIS questions). On the other hand, the mFIS has 5 answer categories per question, whereas the U-FIS only has 4. Hence the naive analysis of the data recorded with the unvalidated draft version of the U-FIS (i.e. the mFIS) as if they had been recorded with the questionnaire for the U-FIS is inadequate, and, overall, the results on U-FIS from the TRANSFORMS study reported by the company cannot be interpreted in a meaningful way. The supplementary information provided by the company did therefore not change the conclusions of the dossier assessment A14-21 on the outcome "fatigue".

2.3 Summary and conclusion

In summary, neither the supplementary information on AEs nor the supplementary information on the recording of fatigue changed the conclusions of dossier assessment A14-21: An added benefit of fingolimod versus IFN-β in subpopulation 1 (patients with highly active RRMS, full previous treatment with disease-modifying therapy [other than IFN-β]) is not proven.

The G-BA decides on the added benefit.

3 References

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