IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A12-06

Fampridine –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Fampridin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 26.04.2012). 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:
Fampridine – Benefit assessment according to § 35a Social Code Book V

Contracting agency:
Federal Joint Committee

Commission awarded on:
01.02.2012

Internal Commission No.:
A12-06

Address of publisher:
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
www.iqwig.de

Medical and scientific advice:

- Jürgen Koehler, Marianne Strauß Hospital, Berg, 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. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Anette ten Haaf
- Kirsten H. Herrmann
- Andreas Gerber
- Ulrich Grouven
- Thomas Kaiser
- Volker Vervölgyi
- Siw Waffenschmidt

Keywords: fampridine, multiple sclerosis, benefit assessment

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

Table of contents

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MS	multiple sclerosis
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 01.02.2012, in accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the benefit assessment of the drug fampridine. 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 01.02.2012.

Research question

The benefit assessment of fampridine was carried out according to its approval status for the following therapeutic indication: improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (EDSS (Expanded Disability Status Scale) 4-7).

The G-BA specified physiotherapy corresponding to the (German) Guideline on Remedies ("Heilmittelrichtlinie") as the appropriate comparator therapy (ACT). Patients were also required to receive optimized standard therapy for MS (including symptomatic treatment with spasmolytics, if necessary).

The company followed in principle the G-BA's specification regarding the ACT and designated continuous physiotherapy with the aim of improving walking as ACT for the above-named therapeutic indication. However, the company deviated in important details from the G-BA's specification. Firstly, it did not address the extent to which the physiotherapy used as ACT in the studies it submitted conformed to the physiotherapy described in the Guideline on Remedies as specified by the G-BA or, if this was not the case, whether it was nevertheless meaningful to consider the individual studies. Secondly, the company gave no details about the required optimized standard therapy for MS. These deviations were not justified by the company. The Institute used the ACT specified by the G-BA for the benefit assessment of fampridine.

Results

The company presented no direct comparative studies on the research question in its dossier, but undertook a non-adjusted indirect comparison between fampridine and physiotherapy on the basis of randomized and non-randomized controlled trials. As a rule, non-adjusted indirect comparisons are not a valid method of analysis, which is why, at the most, conclusions from such analyses can only be drawn in exceptional cases (dramatic effects). However, dramatic effects cannot be deduced from the non-adjusted indirect comparison presented by the company for the research question of this benefit assessment.

Notwithstanding this, the two randomized controlled trials (RCTs) on physiotherapy used by the company are also unsuitable for a non-adjusted indirect comparison. It is highly probable

that a large proportion of the population investigated in the two studies did not correspond to the population relevant for the benefit assessment. In both studies, patients with a very low EDSS score (from 2 or 1.5) could also be enrolled, whereas the treatment with fampridine is only approved for patients with an EDSS score of 4 to 7. The populations investigated in the studies on fampridine or physiotherapy were not sufficiently similar for their results to be compared, because the degree of disability differed markedly. Subgroup analyses for the population of interest were also not presented. In addition, none of the studies state whether the patients had received an optimized standard therapy for MS in accordance with the ACT specified by the G-BA. Moreover, the company did not state how far the physiotherapy used in the studies on the ACT corresponded to the Guideline on Remedies or if this was not the case, whether it was nevertheless meaningful to consider the individual studies.

In summary, there are no evaluable studies on the ACT and hence no evaluable indirect comparison for the assessment of the added benefit of fampridine. Hence, there is no proof of an added benefit of fampridine over the ACT.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug fampridine is assessed as follows:

On the basis of the data available, there is no proof of an added benefit of fampridine in comparison with the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of fampridine was carried out according to its approval status for the following therapeutic indication: "*improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7)*" [1].

The company followed in principle the G-BA's specification regarding the ACT and designated continuous physiotherapy with the aim of improving walking as ACT for the above-named therapeutic indication. However, the company deviated in important details from the G-BA's specification, which determined physiotherapy corresponding to the Guideline on Remedies as the ACT. Patients were also required to receive an optimized standard therapy for MS (including symptomatic treatment with spasmolytics if necessary). Firstly, the company did not address the extent to which the physiotherapy used as ACT in the studies it submitted conformed to the physiotherapy described in the Guideline on Remedies or, if this was not the case, whether it was nevertheless meaningful to consider the individual studies. Secondly, the company gave no details about the required optimized standard therapy

for MS. These deviations were not justified by the company. A detailed explanation can be found in Section 2.7.1 of the full dossier assessment.

The ACT specified by the G-BA was used in this dossier assessment for the benefit assessment of fampridine:

- Physiotherapy corresponding to the Guideline on Remedies. Patients were also required to receive an optimized standard therapy for MS (including symptomatic treatment with spasmolytics if necessary).

The assessment was carried out with respect to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled from the following data:

- Studies on fampridine completed by the company up to 03.11.2011 (study list of the company).
- Results of a bibliographical literature search and a search in trial registries for studies on fampridine (last search 23.01.2012 in bibliographical databases and 21.11.2011 in trial registries, searches by the company)
- Results of a bibliographical literature search and a search in trial registries for studies on the ACT "Treatment with physiotherapy" (last search 18.11.2011 in bibliographical databases and 21.11.2011 in trial registries, searches by the company)

No relevant study was identified from the above-named steps of information retrieval for the present research question for the following reasons:

The company presented no direct comparative studies. All the identified RCTs on fampridine were placebo-controlled and, by themselves, not adequate to demonstrate an added benefit compared to the ACT.

The company undertook an indirect comparison between fampridine and physiotherapy and identified 2 RCTs and 2 non-randomized studies (a single-arm pilot study and a two-arm cohort study) on physiotherapy.

The company carried out no adjusted indirect comparison because it considered the methodological requirement of a common intermediate comparator was not met. As a substitute, the company undertook a non-adjusted indirect comparison. Because the randomization was not considered, such a comparison is associated with a very high degree of uncertainty and is adequate for drawing conclusions for the benefit assessment only in

exceptional cases [2,3]. One such case could be the presence of a dramatic effect. However, this does not apply to the present benefit assessment (see Section 2.7.2.6.1 of the full dossier assessment). Notwithstanding this, the RCTs on physiotherapy are also unsuitable for a non-adjusted indirect comparison. It is highly probable that a large proportion of the population investigated in the two studies did not correspond to the population relevant for the benefit assessment (see Section 2.7.2.3.1 of the full benefit assessment). In both studies, patients with a very low EDSS score (from 2 or 1.5) could also be enrolled, whereas the treatment with fampridine is only approved for patients with an EDSS score of 4 to 7. The populations investigated in the studies on fampridine and on physiotherapy were not sufficiently similar for their results to be compared, because the degree of disability differed markedly. Subgroup analyses for the population of interest were also not presented. In addition, none of the studies state whether the patients had received an optimized standard therapy for MS in accordance with the ACT specified by the G-BA. As regards the studies on the ACT, the company also failed to state whether the physiotherapy was in accordance with the Guideline on Remedies.

The search for non-randomized controlled trials showed fundamental deficiencies, because the relevant outcomes were also included by the company in the search strategy. This type of search is basically unsuitable for identifying relevant publications with adequate sensitivity (see Section 2.7.2.3.1 of the full dossier assessment).

Overall, no study of relevance to the research question is available.

Further information about the inclusion criteria for studies in the benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.4 Results concerning added benefit

No studies relevant for the research question of the benefit assessment were available, either for a direct comparison or for an indirect comparison. Hence, there is no proof of an added benefit of fampridine over the ACT specified by the G-BA.

Further information about the results concerning added benefit can be found in Module 4, Sections 4.3.1.3 of the dossier.

2.5 Extent and probability of the added benefit

On the basis of the available data, there is no proof of an added benefit of fampridine in comparison with the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company’s assessment, which overall derived an indication of a considerable added benefit of fampridine from the results on the non-adjusted indirect comparison between fampridine and the ACT.

The decision regarding added benefit is made by the G-BA.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4.2 of the dossier and in Section 2.7.2.5.2 of the full dossier assessment.

2.6 List of included studies

Not applicable, as the company did not present studies in its dossier from which an added benefit of fampridine over the ACT specified by the G-BA can be determined.

References

(for English extract; (please see full dossier assessment for full reference list)

1) Product information. 20/07/2011 Fampyra -EMEA/H/C/002097 -N/003 Annex I – Summary of Product Characteristics. [Accessed on: 19.08.2012]. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002097/human_med_001432.jsp&mid=WC0b01ac058001d124

2) Bender R, Schwenke C, Schmoor C, Hauschke D. Stellenwert von Ergebnissen aus indirekten Vergleichen: gemeinsame Stellungnahme von IQWiG, GMDS und IBS-DR [Relevance of results from indirect comparisons: conjoint comment from IQWiG, GMDS and IBS-DR] [online]. 02.02.2012 [Accessed on: 14.03.2012]. URL: https://www.iqwig.de/download/12-03-07_Gemeinsame_Stellungnahme_IQWiG_GMDS_IBS-DR_zum_indirekten_Vergleich.pdf.

3) Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R et al. Indirect comparisons of competing interventions. Health Technol Assess 2005; 9(26): iii-iv, 1-134.

The full report (German version) is published under www.iqwig.de.