IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Fidaxomicin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 11.04.2013). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AM-NutzenV	*Arzneimittel-Nutzenbewertungsverordnung* (Regulation for Early Benefit Assessment of New Pharmaceuticals)
CDAD	*Clostridium difficile*-associated diarrhoea
CDI	*Clostridium difficile* infection
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
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 fidaxomicin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 15.01.2013.

Research question

The aim of this report is to assess the added benefit of fidaxomicin according to its approval for the following therapeutic indication: treatment of *Clostridium difficile* infections (CDI) also known as *Clostridium difficile*-associated diarrhoea (CDAD).

The G-BA specified the following appropriate comparator therapy (ACT):

1) in mild CDAD requiring treatment: metronidazole
2) in severe CDAD: vancomycin
3) in recurrent CDAD: vancomycin

The company concurred with the G-BA's specification, but only presented results on the comparison of fidaxomicin with vancomycin as ACT. Hence the dossier did not contain any presentation of a comparison of fidaxomicin with metronidazole.

This benefit assessment considered results on patient-relevant outcomes of direct comparative randomized controlled trials (RCTs) with a minimal duration of 38 days. This concurred with the company's approach.

Results

There were no data on the research question of the added benefit of fidaxomicin in comparison with metronidazole in mild, i.e. all non-severe CDI requiring treatment.

2 relevant studies (studies 101.1.C.003 and 101.1.C.004) were available on the direct comparison of fidaxomicin with vancomycin. These were 2 RCTs, both of them approval studies of fidaxomicin. Patients of 16 years of age or older with a diagnosis of CDI defined by the presence of diarrhoea and the detection of *Clostridium difficile* toxin A or B were enrolled. The studies consisted of a 10-day treatment phase and a subsequent 4-week follow-up phase. Because a large part of the patients (at least 47%) enrolled in the studies had non-severe and non-recurrent CDI requiring treatment, the studies were not relevant as a whole. The benefit assessment was therefore mainly based on the results of the patients with severe

or recurrent CDI, and the results of the total population of the studies were only presented as additional information.

This deviates substantially from the company's approach, which primarily used the results of the total population. The company considered severity and recurrence of the disease as relevant subgroup characteristics and presented the individual results of the subgroups investigated only for those outcomes in which the respective characteristic produced at least an indication of an effect modification (p-value of interaction tests < 0.2). If there was no proof or indication of interactions by the severity or recurrence of the disease, the company applied the results of the total population to the subpopulations of severe and recurrent cases. The approach to present the results of the relevant subpopulations only if there were indications of an effect modification was assessed as inadequate because the research question of this benefit assessment explicitly referred to the subpopulations, and an interaction test alone is unsuitable to prove equivalence.

The risk of bias was rated as low both at study level and, regarding the outcomes considered, at outcome level.

Mortality (outcome: "all-cause mortality")

There were no data on the comparison of fidaxomicin with vancomycin for the outcome "all-cause mortality" in the relevant subpopulation with severe course of disease. It is therefore unclear whether fidaxomicin has an advantage or disadvantage versus vancomycin in this subpopulation.

As in the total population of the studies included, there was no statistically significant difference between the treatment groups in the relevant subpopulation of patients with recurrent course of disease.

In summary, an added benefit of fidaxomicin for patients with recurrent course of disease in comparison with the ACT regarding mortality is not proven. There was no corresponding analysis for the relevant subpopulation with severe course of disease.

Morbidity (outcome: “global cure”)

There were data on the outcome "global cure" regarding the comparison of fidaxomicin with vancomycin for the relevant subpopulation, differentiated according to patients with severe and with recurrent course of disease. The proportion of patients who were rated as cured after the 10-day treatment and who at the same time remained recurrence-free until the end of the follow-up period was recorded. This outcome takes into account the outcomes "cure" and "recurrence" reported by the company, but at the same time allows assessing the entire relevant period, i.e. including an adequate follow-up.

There was no statistically significant difference between the treatment groups for the subpopulation of patients with severe course of disease and for patients with recurrent course

of disease, with the effect estimates showing numerically in the direction in favour of fidaxomicin. In the total population, there was a statistically significant difference in favour of fidaxomicin, however. Due to the lack of indications of an effect modification by severity or recurrence and due to a similar position of the effect estimates it was assumed that the statistical significance in the total population could be applied to the subpopulations. On the basis of the available results there was therefore proof of an added benefit of fidaxomicin. However, since the assessment was largely based on results of a population that was not relevant, the extent was "non-quantifiable".

Hence there is proof of an added benefit in favour of fidaxomicin versus vancomycin regarding the outcome "global cure" for the population of patients with severe or recurrent course of disease.

Quality of life

None of the studies included recorded the outcome "health-related quality of life".

Adverse events

There were no results on adverse events (AEs) for the subpopulations with severe or recurrent course of disease relevant for the comparison of fidaxomicin versus vancomycin in the dossier. The results of the total population of the studies included are therefore only presented as additional information to gain an impression of the possible harm of fidaxomicin in comparison with the ACT.

The meta-analysis did not show a statistically significant difference between fidaxomicin and vancomycin for the overall rate of AEs that led to treatment discontinuation. There was no statistically significant difference between the treatment groups regarding serious AEs (SAEs), either. The effect estimate of the meta-analysis showed in the direction of a numerical disadvantage of fidaxomicin with an overall high proportion of patients with SAEs. Against this background, greater harm from fidaxomicin in comparison with vancomycin could not be excluded without the results of the relevant subpopulations.

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

The overall conclusion on the extent of added benefit for the relevant subpopulations of patients with non-severe CDI requiring treatment and of those patients with severe or recurrent CDI versus the respective ACT is shown separately.

Patients with recurrent or severe CDI

Regarding the positive effects there was proof of an added benefit of fidaxomicin for the outcome "global cure" on the research question of the added benefit of fidaxomicin in comparison with vancomycin in severe or recurrent CDI. There was no statistically significant difference for the relevant subpopulations (with severe or recurrent course of disease), but there was one for the total population. Due to the lack of indications of an effect modification by severity and due to a similar position of the effect estimates it was assumed that the statistical significance in the total population could be applied to the subpopulations. Hence a proof of added benefit of fidaxomicin in severe or recurrent CDI versus the ACT could be derived. The extent is "non-quantifiable", however, against the background of the result of the total population it is not more than "considerable". Regarding the negative effects, greater harm from fidaxomicin cannot be excluded. The company did not submit any data regarding AEs for the relevant subpopulation. As this also concerns SAEs, there is no sufficient proof that the positive effects outweigh the negative effects. There were no results on the outcome "all-cause mortality" for the relevant subpopulation of patients with severe CDI, either. Overall, an added benefit of fidaxomicin for patients with severe or recurrent CDI is not proven.

Patients with non-severe CDI requiring treatment

The company did not present any data on the research question of the added benefit of fidaxomicin in comparison with metronidazole in non-severe CDI requiring treatment. The added benefit of fidaxomicin in comparison with the ACT for these patients is not proven.

The overall assessment deviates substantially from that of the company, which claimed proof of a considerable added benefit for patients with severe or recurrent CDI.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

[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 1-3 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].

2.2 Research question

The added benefit of fidaxomicin was conducted according to the approval [3] for the following therapeutic indication: treatment of CDI, also known as CDAD [3].

The G-BA specified the following ACT:

1) in mild CDAD requiring treatment: metronidazole
2) in severe CDAD: vancomycin
3) in recurrent CDAD: vancomycin

The company concurred with the G-BA's specification, but only presented results on the comparison of fidaxomicin with vancomycin as ACT. Therefore no data were available on the research question of the added benefit of fidaxomicin in comparison with metronidazole in mild CDI requiring treatment. Hence the company did not claim an added benefit for this patient population. Concurring with the company's interpretation with reference to the consultation with the G-BA on the ACT, "mild course of disease requiring treatment" is understood in the context of this benefit assessment to include all those courses of disease that require treatment, but do not fulfil the criteria for a severe or recurrent course of disease. Hereinafter, the term "non-severe course of disease requiring treatment" will be used for this subpopulation.

This benefit assessment considered results on patient-relevant outcomes of direct comparative RCTs with a minimal duration of 38 days. This concurred with the company’s approach.

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 on the basis of the following information:

Sources of the company in the dossier:

- study list on fidaxomicin (studies completed up to 18.10.2012)
- bibliographical literature search and search in trial registries for studies on fidaxomicin (last search in bibliographical databases 23.10.2012, and in trial registries 26.10.2012)

The Institute's own search:

- search in trial registries for studies on fidaxomicin to check the search results of the company (last search 25.01.2013)

This check produced no deviations from the study pool presented in the dossier. However, the studies included by the company were only partly relevant for the benefit assessment (see also nextSection 2.3.1).

Further information on the inclusion criteria for studies in this 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.

2.3.1 Studies included

The approval studies 101.1.C.003 and 101.1.C.004 listed in the following table were included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison – fidaxomicin vs. vancomycin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
101.1.C003	yes	yes	no
101.1.C004	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved RCT: randomized controlled trial; vs.: versus			

The company neither included a study on the direct comparison of fidaxomicin and metronidazole nor conducted a corresponding indirect comparison. Therefore no results were available on the research question of the added benefit of fidaxomicin versus metronidazole in non-severe courses of disease requiring treatment.

The study pool for the benefit assessment of fidaxomicin in comparison with vancomycin in severe or recurrent CDI concurred with the study pool of the company. However, only the results of subpopulations of the 2 included studies were relevant for the assessment of fidaxomicin in comparison with vancomycin because the ACT specified by the G-BA was differentiated according to patient groups.

The main reason for this is that patients with neither severe nor recurrent course of disease were enrolled in the 2 studies (see Section 2.3.2). But the ACT specified by the G-BA for these patients is not the comparator vancomycin, which was used in the study, but metronidazole.

Hence the results of the subpopulations of patients with severe or recurrent course of disease, which are relevant for the comparison with vancomycin, were relevant for the benefit assessment.

This deviates substantially from the company's approach, which primarily used the results of the total population. Accordingly, with few exceptions, the company only presented the results of the total populations of the 2 studies in Module 4 of the dossier. The company considered the severity of the disease and prior occurrence of CDI (recurrence) as relevant subgroup characteristics. The company presented the individual results of the subgroups investigated only for those outcomes in which the respective characteristic produced at least an indication of an effect modification (p-value of interaction tests < 0.2). If there was no proof or indication of interactions by the severity or recurrence of the disease, "the results of the total population can be applied to the subpopulations of severe and recurrent cases", stated the company (Module 4, Section 4.3.1.3.3). In addition, it is necessary to know the results in the subpopulations to exclude interaction. The company, however, concluded an equivalence of the results regarding the total population and the relevant subpopulation from the p-value of an interaction test alone, without considering the individual results of the relevant subpopulations from both studies. This approach by the company was not accepted as the research question of this benefit assessment explicitly referred to the subpopulations, and an interaction test alone is unsuitable to prove the equivalence (see Sections 2.7.2.2 and 2.7.2.3.2 of the full dossier assessment).

For this benefit assessment, the results of the relevant subpopulations on the relevant outcomes "global cure" and "mortality", if available, and, in addition, those of the total population, are presented below. There are no results on AEs for the relevant subpopulations. Therefore, the results of the respective data of the total populations of the 2 studies are also presented to gain an impression of the results of a possible harm from fidaxomicin in comparison with vancomycin and thus increase the transparency of the assessment.

Section 2.6 contains a list of the data sources cited by the company for the studies included by the Institute.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Characteristics of the studies and of the interventions

Table 3 and Table 4 describe the 2 studies included in the benefit assessment. The studies 101.1.C.003 and 101.1.C.004 are double-blind RCTs with almost identical study design. About 600 patients of 16 years of age or older with a diagnosis of CDI defined by the presence of diarrhoea and the detection of *Clostridium difficile* toxin A or B participated in each of the studies. Patients received treatment with fidaxomicin (200 mg twice a day) or vancomycin (125 mg four times a day) in a ratio of 1:1 for 10 days, followed by a follow-up period of 4 weeks. The studies were conducted in North America (101.1.C.003) and North America and Europe (101.1.C.004). "Cure" was the primary outcome after the end of the treatment phase. The secondary outcomes relevant for this benefit assessment were "global

cure at the end of the study", "mortality", "SAEs" and "AEs that led to treatment discontinuation".

This benefit assessment is based on the definition of "severe course of disease" planned a priori in the studies. Patients with more than 9 unformed stools and 15,000 or more leucocytes per µl were rated as having severe course of disease. This deviated from the company's approach, which specified different criteria of severity post hoc in Module 4 of the dossier. Both classifications of severity were considered equivalent for the benefit assessment, but relevant results on the subpopulation of patients with severe course of disease were only available for the predefined definition of severity (see Section 2.7.2.2 of the full dossier assessment).

The total population of the 2 studies did not correspond in its entirety to the population relevant for this benefit assessment as both patients with severe or recurrent course of disease and patients with non-severe CDI requiring treatment were enrolled. About 37% of the participants had severe course of disease and 16% had CDI recurrence at enrolment in the study (see Table 5). There was no information about the extent to which these relevant subpopulations overlapped. Hence the total population of the 2 studies consisted of at least 47% of patients with neither severe nor recurrent course of disease. This means that a large part of the population investigated in the studies was not relevant for the research question of the added benefit of fidaxomicin in comparison with vancomycin.

According to the exclusion criteria of the studies, patients with very severe ("fulminant") CDI were excluded (white blood cell count $> 30 \times 10^9$/L, temperature > 40°C, systolic blood pressure < 90 mmHg, septic shock, peritoneal signs, significant dehydration). Patients with more than one additional CDI episode in the previous 3 months, i.e. with multiple recurrent course of disease, were also not enrolled. Hence there were no relevant data for these patients.

Table 3: Characteristics of the studies included – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomesa
101.1.C003	RCT, double-blind, parallel	Teenagers and adults of 16[b] years of age or older with CDI	Relevant subpopulations: Patients with severe CDI[c] fidaxomicin (n = 112) vancomycin (n = 123) Patients with recurrent CDI[d] fidaxomicin (n = 48) vancomycin (n = 54) Total population: fidaxomicin (N = 302) vancomycin (N = 327)	Treatment: 10 days Follow-up: 28 days ± 2 days	23 centres in Canada and 79 centres in the USA 5/2006 – 8/2008	Primary: cure Secondary: global cure, mortality, AEs
101.1.C004	RCT, double-blind, parallel	Teenagers and adults of 16[b] years of age or older with CDI	Relevant subpopulations: Patients with severe CDI[c] fidaxomicin (n = 90) vancomycin (n = 88) Patients with recurrent CDI[d] fidaxomicin (n = 40) vancomycin (n = 36) Total population: fidaxomicin (N = 270) vancomycin (N = 265)	Treatment: 10 days Follow-up: 28 days ± 2 days	11 centres in Canada, 30 centres in the USA, and 45 centres in Europe 4/2007 – 12/2009	Primary: cure Secondary: global cure, mortality, AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the available outcomes relevant for this benefit assessment.
b: 18 years was determined as the minimum age by a change in the study protocol in the German study centres.
c: Classification of severity planned a priori, see Section 2.3.2
d: Exactly one previous CDI episode in the last 3 months before enrolment in the study
AE: adverse event; CDI: *clostridium difficile* infection; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Fidaxomicin	Vancomycin	Concomitant medication
101.1.C003	2 x 200 mg/day	4 x 125 mg/day	Other drugs that can be used for the treatment of CDI (such as rifaximin) were only allowed to be given in case of failure of the primary treatment or in recurrence. The study patient could still participate in the study if he or she did not receive more than 4 individual doses of metronidazole and/or vancomycin in a total treatment time of not more than 24 hours.
101.1.C004	2 x 200 mg/day	4 x 125 mg/day	Other drugs that can be used for the treatment of CDI (such as rifaximin) were only allowed to be given in case of failure of the primary treatment or in recurrence. The study patient could still participate in the study if he or she did not receive more than 4 individual doses of metronidazole and/or vancomycin in a total treatment time of not more than 24 hours.
CDI: *Clostridium difficile* infection; RCT: randomized controlled trial; vs.: versus			

Characteristics of the study populations

The dossier did not contain information on the characteristics of the relevant subpopulations of patients with severe or recurrent CDI. This would have been worthwhile, however, as it can be assumed that there were considerable differences in the composition of the subpopulations versus the total population, particularly due to the correlation of the severity of the disease with age and hospitalization.

Due to the lack of information on the relevant subpopulations, only the characteristics of the total populations of the included studies 101.1.C.003 and 101.1.C.004 are shown in Table 5. The patients were 62 years old on average, and the proportion of women (58%) was slightly higher than that of men (42%). A little more than one third of the patients was treated as outpatients, the other part as inpatients. As described above, about 37% of the patients had severe, and about 16% had recurrent course of disease. There were no relevant differences between the treatment groups of the studies regarding the distribution of the patient characteristics mentioned.

Table 5: Characteristics of the study populations – RCT, direct comparison: fidaxomicin vs. vancomycin

Study Group	N[a]	Age [years] mean (SD)	Sex [f/m] %	Severity severe/non-severe[b] %	Recurrence recurrent/ non-recurrent %	Type of treatment outpatient/ inpatient %	Study discontin-uations n (%)
101.1.C003							
Fidaxomicin	287	60 (17)	57.1 / 42.9	39.0 / 61.0	16.7 / 83.3	41.8 / 58.2	37 (12.3)[d]
Vancomycin	309	63 (17)	54.7 / 45.3	39.8 / 60.2	17.5 / 82.5	39.5 / 60.5	52 (15.9)[d]
101.1.C004							
Fidaxomicin	252	64 (18)	58.7 / 41.3	35.7 / 63.1[e]	15.9 / 84.1	31.0 / 69.0	57 (21.1)[d]
Vancomycin	257	62 (18)	63.0 / 37.0	34.2 / 65.4[e]	14.0 / 86.0	32.7 / 67.3	51 (19.2)[d]

a: Number of patients in the intention-to-treat population, there were no data for the relevant subpopulations of the study (see Sections 2.3.1 and 2.4).
b: Classification of severity planned a priori, see Section 2.3.2
c: Exactly one previous CDI episode in the last 3 months before enrolment in the study
d: Calculated as the sum of study discontinuations during treatment and follow-up phase. The percentages are based on the number of randomized patients.
e: There was no information on severity for 3 patients in the fidaxomicin group, and one patient in the vancomycin group.
CDI: *Clostridium difficile* infection; f: female; m: male; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There was a clear difference in the proportion of study discontinuations between the 2 studies. About 14% of the patients discontinued treatment in study 101.1.C.003, whereas 20% discontinued treatment in study 101.1.C.004. Moreover, in the latter study, more patients discontinued treatment under fidaxomicin, whereas this was vice versa in study 101.1.C.003.

Risk of bias at study level

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Adequate random sequence generation	Allocation concealment	Blinding: Patient	Blinding: Treating staff	Reporting independent of the results	No additional aspects	Risk of bias at study level
101.1.C003	yes	yes	yes	yes	yes	yes	low
101.1.C004	yes	yes	yes	yes	yes	yes	low

RCT: randomized controlled trial; vs.: versus

The risk of bias at study level was rated as low for both studies included. This concurs with the company's assessment.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and also in Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in this assessment:

- mortality
  - all-cause mortality
- morbidity
  - global cure
- health-related quality of life
- Adverse events
  - overall rate of SAEs
  - overall rate of AEs that led to treatment discontinuation
  - overall rate of AEs (as additional information)

The patient-relevant outcomes chosen deviate from those chosen by the company, which mainly used different outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment for reasons for the choice of outcomes).

Table 7 shows for which outcomes data were available in the studies included.

Table 7: Matrix of outcomes – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Outcomes					
	All-cause mortality	Global cure	Health-related quality of life	AEs	SAEs	Discontinuation due to AEs
101.1.C003	(yes)[a]	yes	–[b]	(yes)[c]	(yes)[c]	(yes)[c]
101.1.C004	(yes)[a]	yes	–[b]	(yes)[c]	(yes)[c]	(yes)[c]

a: There were no data for the relevant subpopulations with severe course of disease (see Sections 2.3.1 and 2.4).
b: Outcome was not recorded.
c: There were no data for the relevant subpopulations (see Sections 2.3.1and 2.4). The results on the AEs for the total population of the study are presented in the benefit assessment as additional information.
AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Results on the outcome "all-cause mortality" were available for patients with recurrent, but not for those with severe course of disease. Results on the outcome "global cure" were available for both relevant subpopulations. None of the studies recorded the outcome "health-related quality of life". No results of the corresponding outcomes regarding AEs were available for the relevant subpopulations.

Table 8 shows the risk of bias for the relevant outcomes.

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Study level	Outcomes					
		All-cause mortality	Global cure	Health-related quality of life	AEs	SAEs	Discontinuation due to AEs
101.1.C003							
Patients with severe CDI[a]	low	–[b]	low	–[c]	–[b]	–[b]	–[b]
Patients with recurrent CDI[d]	low	low	low	–[c]	–[b]	–[b]	–[b]
Total population	low	low	low	–[c]	low	low	low
101.1.C004							
Patients with severe CDI[a]	low	–[b]	low	–[c]	–[b]	–[b]	–[b]
Patients with recurrent CDI[d]	low	low	low	–[c]	–[b]	–[b]	–[b]
Total population	low	low	low	–[c]	low	low	low

a: Classification of severity planned a priori, see Section 2.3.2
b: Risk of bias not assessed as no results on the relevant subpopulation were available.
c: Outcome was not recorded.
d: Exactly one previous CDI episode in the last 3 months before enrolment in the study
CDI: *Clostridium difficile* infection; RCT: randomized controlled trial; vs.: versus

The risk of bias for the outcome "all-cause mortality" and the outcomes concerning AEs was rated as low. This concurs with the company's assessment. The risk of bias for the outcome "global cure", which the company did not present in Module 4, was also rated as low. This assessment applies to the total study populations and for the relevant subpopulations, insofar as corresponding results were available.

Table 9 summarizes the results on mortality and morbidity in the comparison of fidaxomicin with vancomycin in patients with CDI. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. In addition, data from Module 5 of the dossier were added.

Table 9: Results (benefit) – RCT, direct comparison: fidaxomicin vs. vancomycin

Outcome category Outcome Study	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]	p-value
Mortality						
All-cause mortality						
Patients with severe CDI[b]	no data available					
Patients with recurrent CDI[c]					interaction recurrence	0.07
101.1.C003	50	2 (4.0)	55	6 (10.9)	0.37 [0.08; 1.73]	
101.1.C004	43	1 (2.3)	37	3 (8.1)	0.29 [0.03; 2.64]	
Total					0.34 [0.09; 1.21][d]	0.10[d]
Total population						
101.1.C003	300	16 (5.3)	323	21 (6.5)	0.82 [0.44; 1.54]	
101.1.C004	264	20 (7.6)	260	17 (6.5)	1.16 [0.62; 2.16]	
Total					0.98 [0.63; 1.52][d]	0.92[d]
Morbidity						
Global cure						
Patients with severe CDI[b]					interaction severity	0.300[e, f]
101.1.C003	112	80 (71.4)	123	80 (65.0)	0.82 [0.56; 1.19][e]	
101.1.C004	90	64 (71.1)	88	52 (59.1)	0.71 [0.47; 1.06][e]	
Total					0.76 [0.58; 1.01][e, f]	0.058[e, f]
Patients with recurrent CDI[c]					interaction recurrence	0.774[e, f]
101.1.C003	48	33 (68.8)	54	33 (61.1)	0.80 [0.47; 1.37][e]	
101.1.C004	40	30 (75.0)	36	21 (58.3)	0.60 [0.31; 1.16][e]	
Total					0.72 [0.47; 1.09][e, f]	0.115[e, f]
Total population						
101.1.C003	287	214 (74.6)	309	198 (64.1)	0.71 [0.55; 0.91][e]	
101.1.C004	252	193 (76.6)	257	163 (63.4)	0.64 [0.49; 0.84][e]	
Total					0.68 [0.56; 0.81][e, f]	< 0.001[e, f]

a: Patients in analysis
b: Classification of severity planned a priori, see Section 2.3.2
c: Exactly one previous CDI episode in the last 3 months before enrolment in the study
d: Calculated from meta-analysis
e: Values of patients without event: Institute's calculation
f: Institute's calculation, meta-analysis with random effects
CDI: *Clostridium difficile* infection; CI: confidence interval; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

All-cause mortality

There were no data on the comparison of fidaxomicin with vancomycin for the outcome "all-cause mortality" in the relevant subpopulation with severe cause of the disease. It is therefore unclear whether fidaxomicin has an advantage or disadvantage versus vancomycin in this subpopulation.

The meta-analysis of the 2 studies did not show a statistically significant difference between the treatment groups for the relevant subpopulation of patients with recurrent course of disease. This also applies to the total population of the studies included.

In summary, an added benefit of fidaxomicin for patients with recurrent course of disease in comparison with the ACT regarding mortality is not proven. There was no corresponding analysis for the relevant subpopulation with severe course of disease.

Morbidity

Global cure

There were data on the outcome "global cure" regarding the comparison of fidaxomicin with vancomycin for the relevant subpopulation, differentiated according to patients with severe and with recurrent course of disease. The proportion of patients who were rated as cured after the 10-day treatment and who at the same time remained recurrence-free until the end of the follow-up period was recorded (see Section 2.7.2.4.3 of the full dossier assessment for more information on the definition of the outcome).

There was no statistically significant difference between the treatment groups for the subpopulation of patients with severe course of disease or for the patients with recurrent course of disease. The respective effect estimate showed a numerical advantage of fidaxomicin. The meta-analysis of the results for the total population of the 2 studies showed a statistically significant difference in favour of fidaxomicin, however. It was therefore examined to what extent the result of the total population could be used for deriving an added benefit for the relevant subpopulations. This examination was conducted on the basis of a comparison of the position of the effect estimates and on the basis of the p-value for the interaction test.

The results of the meta-analysis on the comparison of fidaxomicin and vancomycin for the outcome "global cure" are presented as a graphic in Figure 1 and Figure 2. Figure 1 provides a presentation differentiated according to severity, i.e. for the subpopulation of patients with severe course of disease and those with non-severe course of disease requiring treatment. Figure 2 shows the analogue meta-analysis differentiated according to recurrence of the disease as additional information.

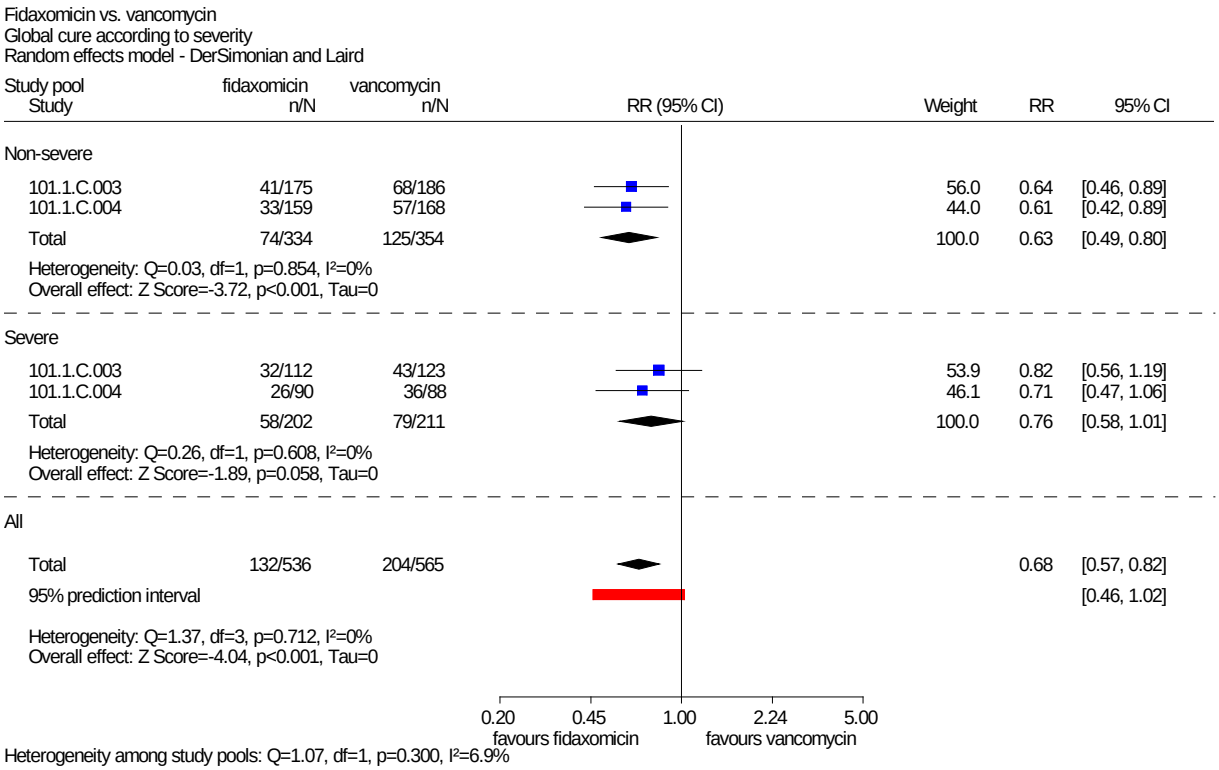

Figure 1: Meta-analysis, global cure according to severity (non-responders): fidaxomicin vs. vancomycin

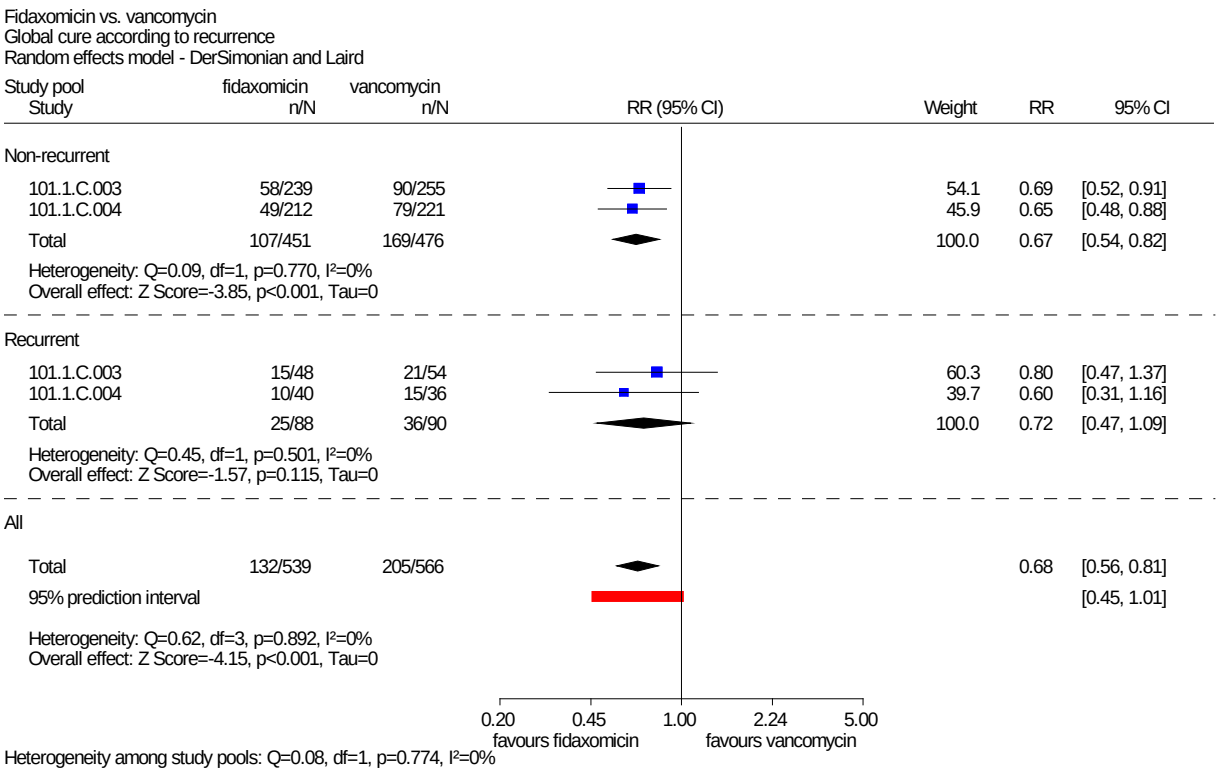

Figure 2: Meta-analysis, global cure according to recurrence (non-responders): fidaxomicin vs. vancomycin

It can be seen that the results of patients with severe CDI did not differ relevantly from those of the total population. The effect estimate of the relative risk for patients with severe CDI is 0.76 and thus closer to the zero effect than the one for the total population (0.68), but this was considered to be sufficiently similar. The absolute risks of global cure are also of a similar magnitude for the subpopulation and the total population (see Table 9). The result of the interaction test does not allow drawing conclusions about relevant differences between the results of the total population and those of the relevant subpopulation, either. The situation was similar when an isolated look was taken at the smaller subpopulation of patients with recurrent CDI. Overall, the result for the total population could be used for deriving an added benefit for the relevant subpopulations. Hence there is proof of an added benefit in favour of fidaxomicin versus vancomycin regarding the outcome "global cure" for the population of patients with severe or recurrent course of disease. However, as this assessment is mainly based on the results of the total population of the studies, and thus to a large extent on patients with non-severe course of disease requiring treatment, the extent of added benefit for patients with severe or recurrent course of disease is non-quantifiable. It might be possible to quantify the result by a joint analysis of the relevant subpopulations (severe and/or recurrent). The company did not provide such an analysis, however, and the data could not be derived from the dossier, either, due to the subpopulations overlapping.

In summary, there is proof of an added benefit of fidaxomicin in comparison with the ACT regarding "global cure" for patients with severe or recurrent course of disease.

Quality of life

None of the studies included recorded the outcome "health-related quality of life", hence there is no proof of added benefit of fidaxomicin in comparison with the ACT regarding this outcome.

Adverse events

There were no results on AEs for the relevant subpopulations with severe or recurrent course of disease in the dossier. The results of the total population of the studies included are therefore presented below as additional information to gain an impression of the possible harm of fidaxomicin in comparison with the ACT. Table 10 shows the corresponding results. The data from the company’s dossier were supplemented, where necessary, by the Institute’s own calculations. In addition, data from Module 5 of the dossier were added.

Table 10: Results (AEs) – RCT, direct comparison: fidaxomicin vs. vancomycin, total population

Outcome category Outcome Study	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]	p-value
Adverse events						
SAEs[b]						
Patients with severe CDI[c]	no data available					
Patients with recurrent CDI[d]	no data available					
Total population						
101.1.C003	300	75 (25.0)	323	78 (24.1)	1.04 [0.79; 1.36]	
101.1.C004	264	70 (26.5)	260	58 (22.3)	1.19 [0.88; 1.61]	
Total					1.10 [0.90; 1.35]	0.35
Discontinuation due to AEs[e]						
Patients with severe CDI[c]	no data available					
Patients with recurrent CDI[d]	no data available					
Total population						
101.1.C003	300	23 (7.7)	323	29 (9.0)	0.85 [0.51; 1.44]	
101.1.C004	264	22 (8.3)	260	20 (7.7)	1.08 [0.61; 1.94]	
Total					0.95 [0.64; 1.40]	0.80
AEs[f]						
Patients with severe CDI[c]	no data available					
Patients with recurrent CDI[d]	no data available					
Total population						
101.1.C003	300	187 (62.3)	323	195 (60.4)		
101.1.C004	264	186 (70.5)	260	177 (68.1)		

a: Patients in analysis
b: Events until the end of the follow-up period
c: Classification of severity planned a priori, see Section 2.3.2
d: Exactly one previous CDI episode in the last 3 months before enrolment in the study
e: Discontinuation due to treatment-related AEs up to 7 days after the end of the treatment
f: Discrepant data between Module 4 and the study reports (without explanation): the values from the study reports are shown, i.e. the treatment-related AEs up to 7 days after the end of the treatment (planned analysis according to protocol).

AE: adverse event; CDI: *Clostridium difficile* infection; CI: confidence interval; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

The meta-analysis did not show a statistically significant difference between fidaxomicin and vancomycin for the overall rate of SAEs and of AEs that led to treatment discontinuation.

The company investigated all outcomes concerning adverse events whether there was an interaction regarding the relevant subpopulations by conducting a subgroup analysis

according to severity or recurrence in the dossier (Module 4). It only presented the p-value of the interaction test, however. This was above 0.2 in all cases. The company concluded from this that the result of the total population could be applied to the relevant subpopulations. This approach was not accepted. An interaction test of $\alpha = 0.2$ alone, which is not statistically significant, is insufficient for drawing a conclusion about the equivalence of effects, justified by the statement that conclusions on a subpopulation were drawn on the basis of results of the total study population (see Section 2.7.2.3.2 of the full dossier assessment). The results of the relevant subpopulations are needed for an assessment, but the company did not present these results.

The lack of these results is also important because SAEs were numerically more frequent under fidaxomicin in both studies.

Regardless of this, there is the additional problem that SAEs caused by the underlying condition CDI were also included in the analysis. This means that also patients with events were analysed who might have been documented by specifically recorded outcomes on morbidity at the same time. Against the background that there was a statistically significant effect in the total population in favour of fidaxomicin in the outcome "global cure", it is conceivable that this covered a possible disadvantage of fidaxomicin regarding SAEs.

In summary, it would therefore be necessary to analyse the relevant subpopulations, if possible without considering events that have already been documented by specifically recorded outcomes on morbidity (global cure), or, at any rate, making this transparent.

Overall, greater harm from fidaxomicin in comparison with vancomycin cannot be excluded because SAEs were numerically more frequent in the total population, and the company's dossier did not contain the corresponding analyses of the relevant subpopulations with severe or recurrent course of disease.

Subgroup analyses

There were no subgroup analyses for the relevant subpopulations of patients with severe or recurrent CDI. The company announced these analyses in Module 4, Section 4.2.5.5, but did not present any corresponding results (see Section 2.7.2.2 of the full dossier assessment).

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level for the two relevant subpopulations. The results of the total population are presented if they can be used for conclusions on the subpopulations considering the different outcome categories and the effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

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 decision on added benefit is made by the G-BA.

2.5.1 Evaluation of added benefit at outcome level

Table 11 shows an assessment on the extent of added benefit of the data presented in Section 2.4 at outcome level for the comparison of fidaxomicin with vancomycin in patients with severe or recurrent CDI. There were no data regarding the comparison of fidaxomicin with metronidazole in patients with non-severe CDI requiring treatment.

Table 11: Fidaxomicin vs. vancomycin – extent of added benefit at outcome level in patients with severe or recurrent CDI

Outcome	**RR [95% CI] p-value probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Patients with severe CDI no data available Patients with recurrent CDI 0.34 [0.09; 1.21] p = 0.10 Total population 0.98 [0.63; 1.52]; p = 0.92	Patients with severe CDI no data available on relevant subpopulation Patients with recurrent CDI: lesser benefit / added benefit not proven
Morbidity		
Global cure[c]	Patients with severe CDI 0.76 [0.58; 1.01] p = 0.058 Patients with recurrent CDI 0.72 [0.47; 1.09] p = 0.115 Total population 0.68 [0.56; 0.81]; p < 0.001 Probability: "proof"	Outcome category: serious/severe symptoms / late complications Added benefit, extent: "non-quantifiable", not more than "considerable"[d]
Health-related quality of life		
–	No data available	Lesser benefit/added benefit not proven
Adverse events		
Overall rate of SAEs	Patients with severe CDI no data available Patients with recurrent CDI no data available Total population 1.10 [0.90; 1.35]; p = 0.35	No data available on relevant subpopulations
Discontinuation due to AE	Patients with severe CDI no data available Patients with recurrent CDI no data available Total population 0.95 [0.64; 1.40]; p = 0.80	No data available on relevant subpopulations

a: Probability provided if statistically significant differences were present
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the CI (CI_o).
c: Values refer to analyses where patients without global cure were counted as event, Institute's calculation, meta-analysis with random effects
d: Considering the result of the - non-relevant - total population (upper limit of the 95% CI at 0.81), the extent of added benefit can be no more than "considerable".
AE: adverse event; CDI: *clostridium difficile* infection; CI: confidence interval; CI_o: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event; vs.: versus

The outcome "global cure" was assigned to the outcome category "serious/severe symptoms / late complications" due to its operationalization. It is important to note here that this outcome, which was called this way in the study, cannot be regarded equivalent with the goal of cure of

the disease cited in the Regulation for Early Benefit Assessment of New Pharmaceuticals (AM-NutzenV) [4].

2.5.2 Overall conclusion on added benefit

The overall conclusion on the extent of added benefit for the relevant subpopulations of patients with non-severe CDI requiring treatment and of those patients with severe or recurrent CDI versus the respective ACT is shown separately.

Patients with recurrent or severe CDI

Table 12 summarizes the results that were considered in the overall conclusion on the extent of added benefit of fidaxomicin versus the ACT vancomycin for patients with severe or recurrent CDI.

Table 12: Positive and negative effects from the assessment of fidaxomicin compared with vancomycin, patients with severe or recurrent CDI

Positive effects	Negative effects
Proof of an added benefit, extent: “non-quantifiable”, no more than "considerable" (serious/severe symptoms / late complications: global cure)	No data available on relevant subpopulation

Regarding the positive effects there was proof of an added benefit of fidaxomicin for the outcome "global cure" on the research question of the added benefit of fidaxomicin in comparison with vancomycin in severe or recurrent CDI. There was no statistically significant difference for the relevant subpopulations (with severe or recurrent course of disease), but there was one for the total population. Due to the lack of indications of an effect modification by severity and due to a similar position of the effect estimates it was assumed that the statistical significance in the total population could be applied to the subpopulations. Hence a proof of added benefit of fidaxomicin in severe or recurrent CDI versus the ACT could be derived. The extent is "non-quantifiable", however, against the background of the result of the total population it is not more than "considerable". Regarding the negative effects, greater harm from fidaxomicin cannot be excluded. The company did not submit any data regarding AEs for the relevant subpopulation. As this also concerns SAEs, there is no sufficient proof that the positive effects outweigh the negative effects. There were no results on the outcome "all-cause mortality" for the relevant subpopulation of patients with severe CDI, either. Overall, an added benefit of fidaxomicin for patients with severe or recurrent CDI is not proven.

Patients with non-severe CDI requiring treatment

The company did not present any data on the research question of the added benefit of fidaxomicin in comparison with metronidazole in non-severe CDI requiring treatment. The added benefit of fidaxomicin in comparison with the ACT for these patients is not proven.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.5.3 Extent and probability of added benefit - summary

An overview of the extent and probability of added benefit in comparison with the ACT for the various subpopulations for which fidaxomicin is approved is given below (see Table 13):

Table 13: Fidaxomicin: extent and probability of added benefit

Subpopulation	**ACT**	**Extent and probability of added benefit**
Patients with non-severe CDI requiring treatment	Metronidazole	Added benefit not proven
Patients with severe or recurrent CDI	Vancomycin	Added benefit not proven
ACT: appropriate comparator therapy; CDI: *Clostridium difficile* infection		

The overall assessment regarding the added benefit of fidaxomicin in patients with non-severe course of disease requiring treatment concurs with that of the company.

Regarding the added benefit of fidaxomicin in patients with severe or recurrent course of disease, the overall assessment deviates substantially from that of the company, which claimed proof of a considerable added benefit for patients with severe or recurrent CDI (see Section 2.7.2.8.2).

2.6 List of included studies

101.1.C.003

Bauer MP, Hensgens MP, Miller MA, Gerding DN, Wilcox MH, Dale AP et al. Renal failure and leukocytosis are predictors of a complicated course of Clostridium difficile infection if measured on day of diagnosis. Clin Infect Dis 2012; 55(Suppl 2): S149-S153.

Bauer MP, Miller M, Gerding DN, Kuijper EJ, Gorbach SL. Renal failure, fever, and leukocytosis all predict treatment failure in Clostridium difficile infection (CDI), but renal failure is the only predictor of recurrent CDI. Clin Microbiol Infect 2011; 17(Suppl 4): A2-A3.

Cornely OA, Miller M, Fantin B, Mullane K, Kean Y, Gorbach S. Clinical outcomes for cancer patients with Clostridium difficile infection. Clin Microbiol Infect 2012; 18(Suppl 3): 672.

Crook DW, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA et al. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. Clin Infect Dis 2012; 55(Suppl 2): S93-S103.

Figueroa I, Johnson S, Sambol SP, Goldstein EJ, Citron DM, Gerding DN. Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin. Clin Infect Dis 2012; 55(Suppl 2): S104-S109.

Gerding D, Crook D, Miller M, Louie TJ, Cornely O, Peto T et al. Factors influencing time to resolution of diarrhea in patients with Clostridium difficile infection treated with fidaxomicin or vancomycin. J Am Geriatr Soc 2012; 60(Suppl 4): S144-S145.

Golan Y, Louie TJ, Miller M, Mullane KM, Weiss K, Lentnek A et al. Risk of recurrence and time to recurrence following treatment of clostridium difficile infection: patient characteristics and the differential effect of fidaxomicin vs. vancomycin. Gastroenterology 2011; 140(5): S360-S361.

Golan Y, Louie TJ, Weiss K, Mullane K, Kean Y, Lentnek A et al. Clostridium difficile recurrence, alcohol consumption, and the effect of fidaxomicin vs vancomycin. Clin Microbiol Infect 2011; 17(Suppl 4): S577.

Golan Y, Mullane K, Louie TJ, Miller M, Weiss K, Lentnek A et al. Immunosuppression and the risk of death, cure rates and disease recurrence among patients with Clostridium difficile infection. Clin Microbiol Infect 2011; 17(Suppl 4): S100-S101.

Louie TJ, Golan Y, Mullane K, Miller M, Crook D, Lentnek A et al. Predictors for treatment failure with fidaxomicin and vancomycin in Clostridium difficile infection. Clin Microbiol Infect 2012; 18(Suppl 3): 671-672.

Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364(5): 422-431.

Miller MA, Kuijper EJ, Gerding DN, Gorbach S. Three simple ESCMID severity criteria predict poor cure rate and slower resolution of diarrhea in Clostridium difficile infection. Clin Microbiol Infect 2010; 16(Suppl s2): S717-S718.

Mullane K, Golan Y, Crook D, Cornely O, Miller M, Louie T et al. Renal impairment and responses to fidaxomicin versus vancomycin in patients with Clostridium difficile infection. J Hosp Med 2012; 7(Suppl 2): S58-S59.

Nerandzic MM, Mullane K, Miller MA, Babakhani F, Donskey CJ. Reduced acquisition and overgrowth of vancomycin-resistant enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. Clin Infect Dis 2012; 55(Suppl 2): S121-S126.

Optimer Pharmaceuticals. A multi-national, multi-center, double-blind, randomized, parallel group study to compare the safety and efficacy of 200 mg PAR-101 taken q12h with 125 mg vancomycin taken q6h for ten days in subjects with Clostridium difficile-associated diarrhea; study 101.1.C.003; clinical study report [unpublished]. 2010.

Weiss K, Louie T, Miller M, Mullane K, Crook D, Esposito R et al. Effect of proton pump inhibitors (PPI) and H2 receptor antagonists (H2RA) on response to therapy with fidaxomicin or vancomycin in hospitalized patients with Clostridium difficile infection. Am J Gastroenterol 2011; 106(Suppl 2): S403.

101.1.C.004

Bauer MP, Hensgens MP, Miller MA, Gerding DN, Wilcox MH, Dale AP et al. Renal failure and leukocytosis are predictors of a complicated course of Clostridium difficile infection if measured on day of diagnosis. Clin Infect Dis 2012; 55(Suppl 2): S149-S153.

Bauer MP, Miller M, Gerding DN, Kuijper EJ, Gorbach SL. Renal failure, fever, and leukocytosis all predict treatment failure in Clostridium difficile infection (CDI), but renal failure is the only predictor of recurrent CDI. Clin Microbiol Infect 2011; 17(Suppl 4): A2-A3.

Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12(4): 281-289.

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Mullane K, Golan Y, Crook D, Cornely O, Miller M, Louie T et al. Renal impairment and responses to fidaxomicin versus vancomycin in patients with Clostridium difficile infection. J Hosp Med 2012; 7(Suppl 2): S58-S59.

Optimer Pharmaceuticals. A multi-national, multi-center, double-blind, randomized, parallel group study to compare the safety and efficacy of 200 mg PAR-101 taken q12h with 125 mg vancomycin taken q6h for ten days in subjects with Clostridium difficile-associated diarrhea; study 101.1.C.004; clinical study report [unpublished]. 2010.

Weiss K, Louie T, Miller M, Mullane K, Crook D, Esposito R et al. Effect of proton pump inhibitors (PPI) and H2 receptor antagonists (H2RA) on response to therapy with fidaxomicin or vancomycin in hospitalized patients with Clostridium difficile infection. Am J Gastroenterol 2011; 106(Suppl 2): S403.

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Please see full dossier assessment for full reference list.

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