Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Fidaxomicin (New Therapeutic Indication: Clostridioides Difficile Infection, Children and Adolescents)

of 3 September 2020

At its session on 3 September 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of fidaxomicin in accordance with the resolution of 4 July 2013 (Federal Gazette, BAnz AT 2 August 2013 B7):

Courtesy translation – only the German version is legally binding.

Fidaxomicin

Resolution of: 3 September 2020
Entry into force on: 3 September 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 14 February 2020):

Dificlir is indicated for the treatment of Clostridioides difficile infections (CDI) also known as C. difficile-associated diarrhoea (CDAD) in adults and paediatric patients from birth to < 18 years of age (see section 4.2 and 5.1).

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

This resolution relates exclusively to children and adolescents under 18 years of age.

Dificlir with the active ingredient fidaxomicin is available in various dosage forms: Film-coated tablets and granules for oral suspension. Fidaxomicin granules for the preparation of an oral suspension are currently not available on the German market. The findings of this resolution shall nevertheless apply to both approved dosage forms.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Patients < 18 years of age with mild courses of Clostridioides difficile-associated diarrhoea requiring treatment

Appropriate comparator therapy:

metronidazole or vancomycin

Extent and probability of the additional benefit of fidaxomicin compared with vancomycin:

An additional benefit is not proven.

b) Patients < 18 years of age with severe and/or recurrent courses of Clostridioides difficile-associated diarrhoea

Appropriate comparator therapy:

vancomycin

Extent and probability of the additional benefit of fidaxomicin compared with vancomycin:

Hint for a considerable additional benefit

Courtesy translation – only the German version is legally binding.

Study results according to endpoints:[1]

a) Patients < 18 years of age with mild courses of Clostridioides difficile-associated diarrhoea requiring treatment

SUNSHINE RCT (single blind, parallel; treatment duration 10 days; observation duration 30 days; fidaxomicin vs vancomycin)

Mortality

Endpoint	**Fidaxomicin**		**Vancomycin**		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality	49	3 (6.1)	17	0 (0)	2.52 [0.14; 46.44]; 0.376[b]

Morbidity

Endpoint Characteristic - Sub-group	**Fidaxomicin**		**Vancomycin**		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Global cure	49	30 (61.2)	17	10 (58.8)	1.04 [0.66; 1.64][c]; 0.863
Effect modification on the endpoint global cure by sex					
male	24	11 (45.8)	8	7 (87.5)	0.52 [0.32; 0.87][h]; 0.013[i]
female	25	19 (76.0)	9	3 (33.3)	2.27 [0.88; 5.88][h]; 0.089[i]
Total				Interaction:	0.007[i]

Endpoint	**Fidaxomicin**		**Vancomycin**		Fidaxomicin vs vancomycin
	N	Median time to event in hours [95% CI] Patients with event n (%)	N	Median time to event in hours [95% CI] Patients with event n (%)	HR [95% CI]; p value[f]
Cessation of diarrhoea[g] (presented additionally)	49	97.0 [39.0; 148.0] 34 (69.4)	17	100.0 [27.0; n.a.] 11 (64.7)	1.27 [0.63; 2.56][h]; 0.508

[1] Data from the dossier assessment of the IQWiG (A20-25) unless otherwise indicated.

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Health-related quality of life

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Endpoint not surveyed					

Side effects

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
AEs[d] (presented additionally)	48	32 (66.7)	16	12 (75.0)	–
SAEs[d]	48	9 (18.8)	16	4 (25.0)	0.75 [0.27; 2.11]; 0.585
Discontinuation because of AEs[e]	48	0 (0)	16	1 (6.3)	0.12 [0.00; 2.71]; 0.107[b]

a. Unless otherwise stated, RR, CI, and p value: logistic regression model, stratified by age
b. Own calculation of RR, CI (asymptotic), and p value (unconditional exact test, CSZ method according to). Because 0 events occurred in one study arm, the correction factor 0.5 was used in both study arms.
c. Own calculation, reversed effect direction, pharmaceutical company reports the effect for the non-occurrence of the event.
d. Contain a relevant proportion of events that can be both side effects and symptomatology of the disease.
e. The reason for the discontinuation was PT vomiting.
f. HR, CI, and p value: Cox Proportional Hazards Model, stratified by age.
g. Duration (recorded in hours, rounding up after ≥ 30 minutes) from the first intake of the study medication until the time of the last episode of watery diarrhoea (patients < 2 years) or the last unformed bowel movement (patients ≥ 2 years to < 18 years), each on the day before the first 2 consecutive days without aqueous diarrhoea or with < 3 unformed bowel movements and durations until the end of the treatment phase.
h. Own calculation, reversed effect direction, pharmaceutical company reports the effect for the non-occurrence of the event.
i. RR, CI, and p value as well as p value of interaction testing from logistic regression model, stratified by sex.

HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	There are no relevant differences for the benefit assessment.
Morbidity	↔	There are no relevant differences for the benefit assessment.

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Endpoint category	Direction of effect/ Risk of bias	Summary
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↔	There are no relevant differences for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

b) Patients < 18 years of age with severe and/or recurrent courses of Clostridioides difficile-associated diarrhoea

SUNSHINE RCT (single blind, parallel; treatment duration 10 days; observation duration 30 days; fidaxomicin vs vancomycin)

Mortality

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality	51	0 (0)	31	0 (0)	-

Morbidity

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Global cure	51	37 (72.5)	31	12 (38.7)	1.89 [1.16; 3.03][b]; 0.009

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Median time to event in hours [95% CI] Patients with event n (%)	N	Median time to event in hours [95% CI] Patients with event n (%)	HR [95% CI]; p value[g]

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Cessation of diarrhoea[h] (presented additionally)	51	42.0 [23.0; 143.0] 40 (78.4)	31	102.0 [45.0; 172.0] 21 (67.7)	1.41 [0.83; 2.44][i]; 0.209

Health-related quality of life

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Endpoint not surveyed					

Side effects

Endpoint	Fidaxomicin		Vancomycin		Fidaxomicin vs vancomycin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
AEs[c] (presented additionally)	50	40 (80.0)	28	21 (75.0)	–
SAEs[c]	50	15 (30.0)	28	8 (28.6)	1.05 [0.51; 2.16]; 0.895
Discontinuation because of AEs[d]	50	1 (2.0)	28	0 (0)	1.71 [0.07; 40.53]; 0.573[e]
Nervous system disorders (SOC, AEs)	50	9 (18.0)	28	0 (0)	OR: 8.19 [1.58; ∞]; 0.014[f]

a. RR, CI, and p value: logistic regression model, stratified by age
b. Own calculation, reversed effect direction, pharmaceutical company reports the effect for the non-occurrence of the event
c. Contain a relevant proportion of events that can be both side effects and symptomatology of the disease
d. The reason for the discontinuation was PT colitis.
e. Own calculation of RR, CI (asymptotic), and p value (unconditional exact test, CSZ method according to). Because 0 events occurred in one study arm, the correction factor 0.5 was used in both study arms.
f. Own calculation using SAS 9.4 (procedure “proc logistic”, statement “exact”, option “exact”), exact conditional logistic regression according to [25]; 1-sided p value
g. HR, CI, and p value: Cox Proportional Hazards Model, stratified by age
h. Duration (recorded in hours, rounding up after ≥ 30 minutes) from the first intake of the study medication until the time of the last episode of watery diarrhoea (patients < 2 years) or the last unformed bowel movement (patients ≥ 2 years to < 18 years), each on the day before the first 2 consecutive days without aqueous diarrhoea or with < 3 unformed bowel movements and durations until the end of the treatment phase
i. Own calculation, reversed effect direction, pharmaceutical company reports the effect for the non-occurrence of the event

HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: Number of patients evaluated; n.c.: not calculable; OR: odds ratio; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

Courtesy translation – only the German version is legally binding.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	There are no relevant differences for the benefit assessment.
Morbidity	↑	Advantages for global cure
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↔	There are no relevant differences for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

a) Patients < 18 years of age with mild courses of Clostridioides difficile-associated diarrhoea requiring treatment

approx. 160 patients

b) Patients < 18 years of age with severe and/or recurrent courses of Clostridioides difficile-associated diarrhoea

approx. 190 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Dificlir™ (active ingredient: fidaxomicin) at the following publicly accessible link (last access: 10 June 2020):

https://www.ema.europa.eu/documents/product-information/dificlir-epar-product-information_de.pdf

4. Treatment costs

Annual treatment costs:

a) Patients < 18 years of age with mild courses of Clostridioides difficile-associated diarrhoea requiring treatment

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Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fidaxomicin 200 mg tablets	€ 1,691.45
Fidaxomicin 40 mg/ml granules[2]	*not quantifiable*
Appropriate comparator therapy:	
Metronidazole	€ 15.02 – 62.64
Vancomycin	€ 107.48 – 432.86

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services: not applicable

b) Patients < 18 years of age with severe and/or recurrent courses of Clostridioides difficile-associated diarrhoea

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fidaxomicin 200 mg tablets	€ 1,691.45
Fidaxomicin 40 mg/ml granules[2]	*not quantifiable*
Appropriate comparator therapy:	
Vancomycin	€ 107.48 – 1,068.33

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 3 September 2020.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 3 September 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

[2] Fidaxomicin granulate 40 mg/ml is currently not available on the German market; a cost presentation is therefore not possible

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