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Activity of Cadazolid and Other Antibiotics against Clinical Isolates of *Clostridium difficile* Collected from European Hospitals in 2014 / 2015

IHMA Europe Sàrl
Rte. de l'Ile-au-Bois 1A
1870 Monthey
Switzerland
imorrissey@ihmainc.com

Ian Morrissey[1], Cyntia De Piano[1], Sophie Magnet[1], Stephen Hawser[1], Timothy W. Morris[2], Hans H. Locher[2]
[1]IHMA Europe Sàrl, Monthey, Switzerland; [2]Actelion Pharmaceuticals Ltd., Allschwil, Switzerland.

INTRODUCTION

- Cadazolid is a novel antibiotic which combines quinolone and oxazolidinone moieties into a new class of antibacterial agents referred to here as quinoxolidinones (1).
- Cadazolid is currently in Phase 3 clinical development for treatment of *Clostridium difficile*-associated diarrhoea (CDAD), also known as *C. difficile* infection (CDI).
- In the Phase 2 trial for treatment of CDAD, cadazolid clinical cure rates were similar to vancomycin with lower recurrence rates, resulting in higher sustained cure rates (3).
- This study evaluated the activity of cadazolid and other antibiotics against recent clinical isolates of *C. difficile* from Europe collected in 2014/2015.

METHODS

- A total of 652 clinical isolates of *C. difficile* were collected in 2014/2015 from 10 European countries (29 sites). Details are provided in Table 1.
- Minimum inhibitory concentrations (MICs) for cadazolid and antibiotic comparators were determined by agar dilution following Clinical and Laboratory Standards Institute (CLSI) guidelines (3). MIC_{50} and MIC_{90} (concentrations to inhibit 50% & 90% of isolates, respectively) were calculated.
- Susceptibility was evaluated using CLSI breakpoints for anaerobes (4), except for vancomycin and metronidazole where the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for *C. difficile* based on epidemiological cut-off values were used (5) (Table 2). Breakpoints for *C. difficile* are not based on clinical efficacy in treatment of CDAD.

Table 1. Isolates investigated by year and by country of collection.

Country (# sites)	Year of collection		Total
	2014	2015	
Belgium (1)	-	20	20
Czech Republic (2)	8	33	41
France (9)	9	118	127
Germany (3)	108	58	166
Hungary (1)	4	25	29
Poland (1)	-	20	20
Romania (3)	-	59	59
Spain (5)	21	94	115
Sweden (1)	-	21	21
United Kingdom (3)	-	54	54
TOTAL	**150**	**502**	**652**

Acknowledgments

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Table 2. Antibiotic breakpoints used in this study.

Antibiotic	Breakpoint (mg/L):			Source
	Susceptible	Intermediate	Resistant	
Cadazolid	**NB**	**NB**	**NB**	-
Vancomycin	≤2	-	≥4	EUCAST (5)
Metronidazole	≤2	-	≥4	EUCAST (5)
Fidaxomicin	NB	NB	NB	-
Rifaximin	NB	NB	NB	-
Tigecycline	NB	NB	NB	-
Clindamycin	≤2	4	≥8	CLSI (4)
Imipenem	≤4	8	≥16	CLSI (4)
Linezolid	NB	NB	NB	-
Moxifloxacin	≤2	4	≥8	CLSI (4)

NB, no breakpoint available.

RESULTS

- Cadazolid was very active against the European *C. difficile* isolates collected in 2014 and 2015 with overall MIC_{50} and MIC_{90} of 0.5 mg/L (Table 3).
- MICs were distributed over a very narrow range between 0.12 and 1 mg/L. Only one isolate (from Spain) had a MIC of 1 mg/L (Figure 1).
- Based on MIC_{90} cadazolid was more potent than vancomycin and metronidazole and equal to fidaxomicin (Table 3).
- Cumulative MIC distribution for cadazolid and comparators against all 652 isolates of *C. difficile* are shown in Figure 2.
- Cadazolid MIC distributions were very consistent between countries with an MIC_{50} and MIC_{90} of 0.5 mg/L, except Sweden where MIC_{50} was 0.25 µg/ml (Table 4).
- The activity of vancomycin, metronidazole, fidaxomicin, tigecycline and linezolid was also consistent between countries (Table 4).
- Susceptibility was very low to imipenem and clindamycin in all countries (Table 4).
- Susceptibility to moxifloxacin was more variable by country ranging from 17% in Romania to 90% in the United Kingdom (Table 4).
- Rifaximin activity varied from country to country, but MIC_{90} was > 16 mg/L in most countries (Table 4)

References

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4. Clinical and Laboratory Standards Institute (CLSI), CLSI document M100-S26. 2016: Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087, USA.
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Table 3. Activity of cadazolid and comparators against all clinical isolates of *C. difficile* (n=652).

Compound	MIC (mg/L):				Percentage		
	MIC_{50}	MIC_{90}	Min	Max	Sus	Int	Res
Cadazolid	**0.5**	**0.5**	**0.12**	**1**	-	-	-
Vancomycin	1	2	≤0.25	4	97.2	-	2.8
Metronidazole	0.5	1	≤ 0.06	4	99.9	0.0	0.2
Fidaxomicin	0.25	0.5	0.03	1	-	-	-
Rifaximin	0.015	> 16	≤0.002	> 16	-	-	-
Tigecycline	0.12	0.12	≤0.015	2	-	-	-
Clindamycin	8	> 32	≤0.06	> 32	7.2	16.4	76.4
Imipenem	> 16	> 16	4	> 16	0.6	7.4	92.0
Linezolid	2	4	≤0.25	32	-	-	-
Moxifloxacin	2	32	≤0.5	> 32	59.8	0.5	39.7

Sus, susceptible; Int, intermediate; Res, resistant.

Figure 2. Cumulative MIC distribution for cadazolid and comparators against clinical isolates of *C. difficile* (n=652).

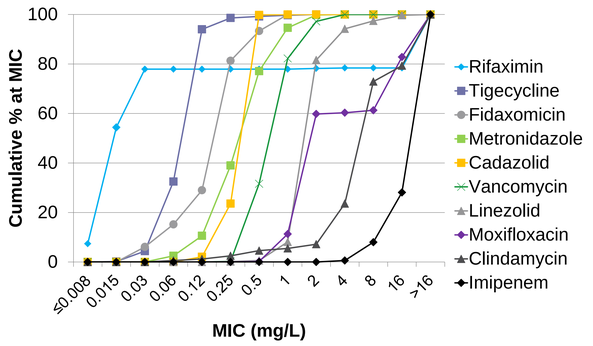
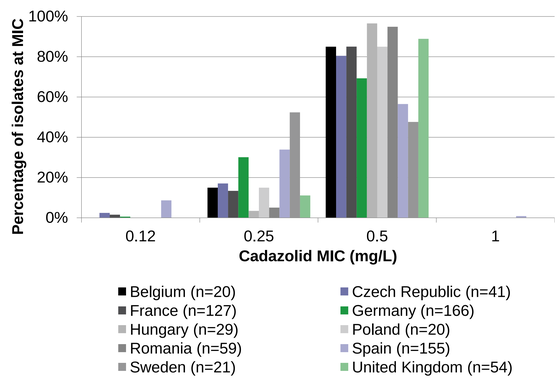


Table 4. Activity of cadazolid and comparators against *C. difficile* isolates by country.

Country (# isolates)	Antibiotic (MIC_{50}/MIC_{90} (% resistant))									
	Cadazolid	Vanco-mycin	Metro-nidazole	Fidaxo-micin	Rifaximin	Tige-cycline	Clinda-mycin	Imipenem	Linezolid	Moxi-floxacin
Belgium (20)	**0.5/0.5**	1/2 (0)	0.25/0.5 (0)	0.25/0.25	0.03/0.03	0.12/0.12	8/8 (70)	>16/>16 (95)	2/2	2/16 (15)
Czech Republic (41)	**0.5/0.5**	1/2 (2.4)	0.5/2 (0)	0.25/1	0.03/>16	0.12/0.25	8/>32 (80.5)	>16/>16 (95.1)	2/16	16/32(56.5)
France (127)	**0.5/0.5**	1/2 (0)	0.5/0.5 (0.8)	0.25/0.25	0.015/0.03	0.12/0.12	8/16 (69.3)	>16/>16 (96.9)	2/4	2/16 (18.1)
Germany (166)	**0.5/0.5**	1/2 (9.6)	0.5/1 (0)	0.25/0.25	0.015/>16	0.12/0.12	16/>32 (94.6)	>16/>16 (83.1)	2/8	2/32 (44.6)
Hungary (29)	**0.5/0.5**	1/2 (0)	1/2 (0)	0.25/1	>16/>16	0.12/0.12	8/16 (93.1)	>16/>16 (100)	2/4	32/32 (69)
Poland (20)	**0.5/0.5**	1/1 (0)	0.5/2 (0)	0.25/0.5	>16/>16	0.12/0.12	8/8 (55)	>16/>16 (100)	2/2	16/32 (55)
Romania (59)	**0.5/0.5**	0.5/1 (0)	1/1 (0)	0.5/1	>16/>16	0.12/0.12	8/8 (79.7)	>16/>16 (100)	2/2	16/16 (83.1)
Spain (115)	**0.5/0.5**	1/1 (0)	0.25/0.5 (0)	0.25/0.25	0.015/>16	0.12/0.12	4/>32 (48.7)	>16/>16 (93.9)	2/4	2/32 (38.3)
Sweden (21)	**0.25/0.5**	0.5/1 (0)	0.25/0.25 (0)	0.25/0.5	0.015/0.03	0.06/0.12	8/8 (66.7)	16/>16 (57.1)	2/2	2/16 (28.6)
United Kingdom (54)	**0.5/0.5**	1/2 (0)	0.5/0.5 (0)	0.25/0.25	0.015/0.015	0.06/0.06	8/16 (94.4)	>16/>16 (98.2)	2/2	2/2 (9.3)

Figure 1. MIC distribution for cadazolid against clinical isolates of *C. difficile* from various European countries.



CONCLUSIONS

- **Cadazolid was very active MIC_{90} (0.5 mg/L) with consistent activity against *C. difficile* isolates from the 10 European countries studied.**
- **Only one isolate had a MIC of 1 mg/L and no cadazolid MIC >1 mg/L was observed for any strain.**
- **Based on MIC_{90} cadazolid was more potent than vancomycin and metronidazole and equal to fidaxomicin.**
- **High resistance was observed to imipenem and clindamycin for *C. difficile* from each country.**
- **Substantial resistance was observed to moxifloxacin in *C. difficile* from most countries with >90% susceptibility only found in isolates from the UK.**
- **The consistent activity of cadazolid against 2014/2015 European isolates supports its continued investigation as a new therapy for *C. difficile*-associated diarrhoea.**

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