New Drug Application NDA 22-171
DORIBAX® (doripenem for injection)

Microbiology: Decrease In Doripenem Susceptibility During Therapy

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Decreased Doripenem Susceptibility

- Decreased susceptibility may lead to treatment failure in nosocomial pneumonia (NP) patients
- Bacteria may be transmitted to other patients (safety concern)
- Observations from review:
  - Large MIC increases during therapy
  - Monte Carlo simulation data
  - *In vitro* resistance selection data
  - Elevated MICs among CF isolates
  - Surveillance data

Decreased Doripenem Susceptibility

- *P. aeruginosa* isolates with a MIC ≤ 2 μg/ml are considered susceptible to doripenem
- No breakpoints for intermediate and resistant
- *What are the consequences of decreased doripenem susceptibility?*

Analysis of NP Isolates with Doripenem MIC Increases –Both Arms, DOR-09

Trial #	Cohort	Patient ID	Organism	DOR MICs Initial	DOR MICs Final	DOR Step Increase	MER Step Increase	Clinical Outcome
DORI-09	DOR	94101007	*S. aureus*	1	16	4	NA	**FAILURE**
DORI-09	DOR	31004017	*P. aeruginosa*	0.25	8	5	NA	**FAILURE**
DORI-09	Pip-tazo	93002031	*S. aureus*	8	32	2	NA	
DORI-09	Pip-tazo	40103009	*K. pneumoniae*	0.25	1	2	NA	
DORI-09	Pip-tazo	20406505	*E. faecalis*	4	16	2	NA	

DOR MIC increases (4-5 steps) associated with clinical failure in non-intubated NP patients treated with DOR

Analysis of NP Isolates with Doripenem MIC Increases –Doripenem Arm, DOR-10

Trial #	Cohort	Patient ID	Organism	DOR MICs Initial	DOR MICs Final	DOR Step Increase	MER Step Increase	Clinical Outcome
DORI-10	DOR	12302047	*P. aeruginosa*	0.12	4	5	5	
DORI-10	DOR	12302566	*P. aeruginosa*	4	32	3	1	
DORI-10	DOR	13402058	*P. aeruginosa*	0.12	4	5	5	
DORI-10	DOR	14401501	*P. aeruginosa*	0.5	8	4	5	
DORI-10	DOR	14402547	*P. aeruginosa*	0.12	1	3	5	
DORI-10	DOR	20506501	*P. aeruginosa*	0.12	4	5	5	
DORI-10	DOR	20506559	*P. aeruginosa*	0.25	2	3	4	
DORI-10	DOR	60203515	*P. aeruginosa*	0.5	8	4	4	
DORI-10	DOR	75306011	*P. aeruginosa*	1	4	2	2	
DORI-10	DOR	50603502	*K. pneumoniae*	0.03	0.12	2	0	
DORI-10	DOR	14402572	*E. aerogenes*	0.03	0.25	3	2	

- **DOR MIC increases (4-5 steps) associated with *P. aeruginosa* infections in intubated NP patients treated with DOR**
- **MER MIC step increases mirror DOR MIC step increases**

Analysis of NP Isolates with Doripenem MIC Increases –Imipenem Arm, DOR-10

Trial #	Cohort	Patient ID	Organism	DOR MICs Initial	DOR MICs Final	DOR Step Increase	MER Step Increase	Clinical Outcome
DORI-10	IMP	1506524	*P. aeruginosa*	0.25	4	4	4	FAILURE
DORI-10	IMP	3106030	*P. aeruginosa*	0.06	1	4	5	
DORI-10	IMP	10902038	*P. aeruginosa*	1	8	3	2	
DORI-10	IMP	11102537	*P. aeruginosa*	0.12	4	5	5	FAILURE
DORI-10	IMP	20106020	*P. aeruginosa*	1	8	3	3	FAILURE
DORI-10	IMP	21006548	*P. aeruginosa*	0.25	2	3	3	
DORI-10	IMP	50203023	*P. aeruginosa*	0.25	2	3	4	
DORI-10	IMP	50204511	*P. aeruginosa*	0.25	4	4	4	
DORI-10	IMP	70406529	*P. aeruginosa*	0.5	4	3	4	
DORI-10	IMP	75406550	*P. aeruginosa*	0.25	2	3	3	
DORI-10	IMP	10701005	*E. aerogenes*	0.06	0.5	3	2	

- **DOR MIC increases (4-5 steps) associated with *P. aeruginosa* infections in intubated NP patients treated with IMP**
- **MER MIC step increases mirror DOR MIC step increases**

Analysis of DOR/MER MICs among Clinical Failures (DOR-09, Doripenem Arm)

		MICs mcg/mL					
PATIENT ID	ORGANISM	DOR INITIAL	FINAL	MER INITIAL	FINAL	(DOR) STEP INCREASE	(MER) STEP INCREASE
17306512	*A. baumannii*	>128	ND	>128	ND	0	ND
31003040	*A. baumannii*	1	ND	0.5	ND	ND	ND
19706124	*K. pneumoniae*	0.06	ND	0.06	ND	0	ND
92102505	*K. pneumoniae*	0.03	ND	0.03	ND	ND	ND
94101007	*E. aerogenes*	0.06	0.12	0.06	0.06	1	1
31003040	*E. coli*	0.03	ND	0.03	ND	ND	ND
401045202	*E. coli*	0.03	ND	≤0.015	ND	ND	ND
40503005	*P. aeruginosa*	0.25	ND	0.12	ND	ND	ND
31004017	*P. aeruginosa*	0.25	8	0.25	8	5	5
19705001	*P. aeruginosa*	1	1	2	2	0	0
94101007	*S. aureus*	1	16	2	32	4	4
17306127	*S. aureus*	0.12	ND	0.25	ND	ND	ND
30003000	*S. aureus*	>32	ND	>32	ND	ND	ND
40503021	*S. aureus*	32	ND	64	ND	ND	ND
40503506	*S. aureus*	0.03	0.03	0.06	0.06	0	ND

Analysis of DOR/MER MICs among Clinical Failures (DOR-09, PIP-TAZO Arm)

		MICs		mcg/mL			
PATIENT ID	ORGANISM	DOR INITIAL	FINAL	MER INITIAL	FINAL	(DOR) STEP INCREASE	(MER) STEP INCREASE
17306132	*A. baumannii*	128	ND	128	ND	ND	ND
18506142	*A. baumannii*	0.5	ND	1	ND	ND	ND
19706514	*A. baumannii*	0.5	ND	0.5	ND	ND	ND
30003026	*A. baumannii*	2	ND	1	ND	ND	ND
19005008	*P. aeruginosa*	0.12	ND	0.06	ND	ND	ND
19205005	*P. aeruginosa*	0.12	0.25	0.12	0.25	0	0
30104505	*P. aeruginosa*	0.25	1	0.12	1	2	3
31204022	*P. aeruginosa*	4	ND	8	ND	ND	ND
40503033	*P. aeruginosa*	0.06	ND	0.03	ND	ND	ND
60706000	*P. aeruginosa*	0.03	0.12	≤0.015	0.06	2	2
19005008	*K. pneumoniae*	0.06	0.12	≤0.015	0.06	1	2
30603500	*K. pneumoniae*	0.06	ND	0.03	ND	ND	ND
31104512	*K. pneumoniae*	0.03	ND	0.03	ND	ND	ND

Analysis of DOR/MER MICs among Clinical Failures (DOR-09, PIP-TAZO Arm, continued)

		MICs mcg/mL					
PATIENT ID	ORGANISM	DOR INITIAL	FINAL	MER INITIAL	FINAL	(DOR) STEP INCREASE	(MER) STEP INCREASE
40103009	*K. pneumoniae*	0.25	0.5	0.25	0.25	1	0
40503033	*K. pneumoniae*	0.25	ND	0.25	ND	ND	ND
400504004	*K. pneumoniae*	0.06	ND	≤0.015	ND	ND	ND
30603500	*E. cloacae*	0.06	ND	0.03	ND	ND	ND
31104512	*M. morganii*	1	ND	0.25	ND	ND	ND
93102011	*E. faecalis*	4	ND	4	ND	ND	ND
40103526	*H. influenzae*	0.03	ND	0.06	ND	ND	ND
40503010	*H. influenzae*	0.12	ND	0.06	ND	ND	ND
93201503	*S. aureus*	4	2	4	4	0	0
31203529	*S. aureus*	32	ND	32	ND	ND	ND
18006044	*S. aureus*	32	ND	64	ND	ND	ND

Analysis of DOR/MER MICs among Clinical Failures (DOR-10, Doripenem Arm)

		MICs mcg/mL					
PATIENT ID	ORGANISM	DOR INITIAL	FINAL	MER INITIAL	FINAL	(DOR) STEP INCREASE	(MER) STEP INCREASE
70406526	*M. morganii*	0.25	ND	0.12	ND	ND	ND
70406526	*K. pneumoniae*	0.03	ND	≤0.015	ND	ND	ND
50103015	*K. pneumoniae*	0.06	ND	0.03	ND	0	0
1606555	*E. cloacae*	≤0.015	≤0.015	≤0.015	≤0.015	0	0
3605538	*E. cloacae*	0.03	0.06	0.03	0.03	1	1
13202052	*E. cloacae*	≤0.015	ND	≤0.015	ND	ND	ND
1606555	*E. coli*	≤0.015	≤0.015	≤0.015	≤0.015	0	0
1806506	*E. coli*	0.03	0.03	0.03	≤0.015	0	0
20406014	*E. coli*	≤0.015	≤0.015	≤0.015	≤0.015	0	0
75306002	*P. aeruginosa*	1	1	2	1	0	0
80205535	*P. aeruginosa*	0.12	16	0.5	16	7	5
12302047	*P. aeruginosa*	0.12	0.25	0.12	0.25	1	1
20106531	*P. aeruginosa*	4	ND	8	ND	ND	ND
21006042	*P. aeruginosa*	2	ND	2	ND	ND	ND

Analysis of DOR/MER MICs among Clinical Failures (DOR-10, Doripenem Arm, continued)

		MICs mcg/mL					
PATIENT ID	ORGANISM	DOR INITIAL	FINAL	MER INITIAL	FINAL	(DOR) STEP INCREASE	(MER) STEP INCREASE
405015	*S. aureus*	≤0.015	64	0.06	64	8	10
13202052	*S. aureus*	≤0.015	0.5	0.06	1	5	4
14402559	*S. aureus**	0.12	0.12	0.25	0.25	0	0
21005510	*S. aureus*	0.03	ND	0.06	ND	ND	ND
21206558	*S. aureus*	≤0.015	≤0.015	0.06	0.06	0	0
50103015	*S. aureus**	32	32	32	32	0	0
50103509	*S. aureus**	16	16	32	32	0	0
51304009	*S. aureus*	0.03	0.03	0.06	0.06	0	0
12302061	*H. influenzae*	0.12	0.12	0.06	0.12	0	1
21105532	*H. influenzae*	0.25	0.25	0.06	0.06	0	0
14402559	*H. influenzae*	0.25	ND	0.06	ND	ND	ND
50203018	*H. influenzae*	0.06	0.06	0.03	0.25	0	3
15202031	*H. influenzae*	0.12	ND	0.12	ND	ND	ND
15202031	*S. pneumoniae*	0.25	ND	0.25	ND	ND	ND

Analysis of DOR/MER MICs among Clinical Failures (DOR-10, Imipenem Arm)

		MICs mcg/mL					
PATIENT ID	ORGANISM	DOR INITIAL	FINAL	MER INITIAL	FINAL	(DOR) STEP INCREASE	(MER) STEP INCREASE
70405520	*S. marcescens*	0.06	0.06	0.03	0.03	0	0
13802053	*E. coli*	0.03	≤0.015	≤0.015	≤0.015	**0**	**0**
14401015	*E. coli*	0.03	ND	0.03	ND	ND	ND
12802521	*E. coli*	0.03	ND	<0.015	ND	ND	ND
12401009	*E. coli*	≤0.015	ND	<0.015	ND	ND	ND
12301505	*E. coli*	0.03	0.03	<0.015	≤0.015	0	0
50104508	*A. baumannii*	0.25	0.5	0.5	1	1	1
14302042	*H. influenzae*	0.06	0.06	≤0.015	≤0.015	0	0
60104518	*H. influenzae*	0.06	0.12	0.06	0.06	1	0
21105524	*H. influenzae*	0.06	0.25	0.03	0.06	2	0
15212030	*H. influenzae*	0.06	ND	0.03	ND	ND	ND
80905533	*K. pneumoniae*	0.03	0.03	0.03	0.03	0	0
50203504	*K. pneumoniae*	0.03	0.03	0.03	<0.015	ND	ND
14402503	*K. pneumoniae*	0.06	ND	0.03	ND	ND	ND
12802521	*K. pneumoniae*	0.03	ND	0.06	ND	ND	ND

Analysis of DOR/MER MICs among Clinical Failures (DOR-10, Imipenem Arm, continued)

		MICs mcg/mL					
		DOR		MER		STEP INCREASE	
PATIENT ID	ORGANISM	INITIAL	FINAL	INITIAL	FINAL	DOR	MER
11102537	*K. oxytoca*	0.03	ND	0.03	ND	ND	ND
14401015	*E. aerogenes*	0.06	ND	0.06	ND	ND	ND
11102537	*E. aerogenes*	0.06	ND	0.06	ND	ND	ND
10701005	*E. aerogenes*	0.06	0.12	0.03	0.03	0	0
15202032	*E. cloacae*	0.03	ND	0.03	ND	0	0
12802521	*E. cloacae*	0.06	ND	0.03	ND	0	0
1806010	*E. cloacae*	0.06	0.06	0.06	0.06	0	0
70406529	*P. aeruginosa*	0.5	0.5	0.5	0.25	0	0
50203023	*P. aeruginosa*	0.25	0.12	0.12	0.12	0	0
21106542	*P. aeruginosa*	0.25	4	0.25	4	4	4
20106530	*P. aeruginosa*	0.25	0.12	0.12	0.12	0	0
20106220	*P. aeruginosa*	1	8	0.5	8	3	4
14401015	*P. aeruginosa*	0.12	0.12	0.06	0.06	0	0

Analysis of DOR/MER MICs among Clinical Failures (DOR-10, Imipenem Arm, continued)

		MICs mcg/mL					
		DOR		MER		STEP INCREASE	
PATIENT ID	ORGANISM	INITIAL	FINAL	INITIAL	FINAL	DOR	MER
13201026	*P. aeruginosa*	8	8	8	16	0	1
1506524	*P. aeruginosa*	0.25	4	0.25	4	4	4
10701003	*P. aeruginosa*	8	8	8	32	0	2
11102029	*P. aeruginosa*	0.12	0.12	0.12	0.12	0	0
11102537	*P. aeruginosa*	0.12	4	0.12	4	5	5
12802549	*Pseudomonas* spp	<0.015	ND	≤0.015	ND	ND	ND
805019	*S. aureus*	<0.015	≤0.015	0.06	0.06	0	0
1806510	*S. aureus*	0.03	≤0.015	0.12	0.06	0	0
12301505	*S. aureus*	0.03	0.03	0.06	0.06	0	0
13802053	*S. aureus*	0.03	ND	0.06	ND	ND	ND
14401015	*S. aureus**	0.25	0.25	0.25	0.5	0	1
14402503	*S. aureus*	0.03	ND	0.06	ND	ND	ND
15202032	*S. aureus**	0.12	ND	0.25	ND	ND	ND
50104508	*S. aureus**	16	16	32	32	0	0
50204501	*S. aureus**	16	8	32	16	0	0
70405519*	*S. aureus*	≤0.015	ND	0.06	ND	ND	ND

Analysis of Clinical Failures among Patients Receiving Doripenem or Comparator

Most patients had either:

- Polymicrobial infections,
- Baseline MICs of ≥ 1mcg/mL
- MRSA infections,
- *Pseudomonas aeruginosa* infections, or
- ≥ 2 increase in doripenem MIC during therapy

Monte Carlo Simulations

- Species-specific target attainment values calculated to determine probability of attaining specific target at selected dose of DOR against specific pathogen
- Time above MIC (T > MIC) is best PK/PD predictor of *in vivo* efficacy
- Summary table for species of interest at 500 mg q8h for a 1 and 4 hour infusion for NP pathogens

Probability of Target Attainment by Organism

Organism	500 mg, q8h, 1 h infusion			500 mg, q8h, 4 h infusion		
	25% T > MIC	30% T > MIC	35% T > MIC	25% T > MIC	30% T > MIC	35% T > MIC
Enterobacteriaceae	99.88	99.75	99.61	99.97	99.97	99.96
P. aeruginosa	89.48	86.31	83.25	92.48	92.06	91.48
Acinetobacter spp.	77.67	76.85	75.43	77.76	77.69	77.61
Haemophilus spp.	100	99.96	99.87	100	100	100
Staphylococcus spp.	86.07	85.39	84.84	86.61	86.44	86.23
S. aureus Oxa-S	100	100	99.99	100	100	100
S. pneumoniae	99.98	99.89	99.63	99.99	99.99	99.99

Target attainment for PA and AS at 35% T > MIC is below level of *in vivo* efficacy

Resistance Development Studies

Pseudomonas serial passage study with doripenem +/- gentamicin

- Doripenem (alone) MIC increases:
  - > 8 fold (3 isolates)
  - 2-fold (1 isolate)
  - unchanged (2 isolates)
- Doripenem + gentamicin MIC increases:
  - 4-fold (1 isolate)
  - 2-fold (2 isolates)
  - unchanged (3 isolates)

Fewer DOR MIC increases when combined with GM

P. aeruginosa Multiple Passage Study

Passage #	DOR MIC DOR	DOR Passage (μg/ml) MEM	DOR Passage (μg/ml) IPM	MEM MIC DOR	MEM Passage (μg/ml) MEM	MEM Passage (μg/ml) IPM	IPM MIC DOR	IPM Passage (μg/ml) MEM	IPM Passage (μg/ml) IPM
1	0.06	0.03	0.5	0.06	0.03	0.5	0.06	0.03	0.5
4	0.25	0.25	0.5	1	0.25	16	0.12	0.12	1
8	4	2	8	4	4	16	2	2	16
12	4	4	16	4	8	16	2	2	16
14	4	4	16	4	8	16	4	4	16

- DOR MIC in *P. aeruginosa* increased 6 dilution steps from 0.06 to 4 mcg/ml
- DOR MIC increases were similar to both MER and IMP

Doripenem MIC_{90s} For Multi-Drug Resistant Isolates

Species	N	MIC_{90} (mcg/ml)	Applicant Reference
Acinetobacter baumannii	33	16	22
(ceftazidime-S)	30	1	3, 28
(ceftazidime-NS)	10	>16	3
Pseudomonas aeruginosa	337	0.5—12.5	21—24, 29
(CF-isolates)	82	2	29
(CF-isolates) mucoid	200	32	33
(CF-isolates) non-mucoid	200	64	33
(beta-lactamase-positive)	15	4	30
(ceftazidime-resistant)	39	8	25
(carbapenem-sensitive)	83	2	25
(carbapenem-resistant)	66	8-- > 32	2, 25
(ciprofloxacin-resistant)	16	8	25
(gentamicin-resistant)	37	8	25
(metallo-beta-lactamases)	15	>32	2
	15	64	30

Surveillance Data

- 17,000 organisms over 3 years (2003—5) from North America, Latin America & Europe
- 20 sites/region
- MICs from North America shown for organisms sought in the NP indication

Surveillance Data

Organism	2003		2004		2005	
	MIC_{90}	Range	MIC_{90}	Range	MIC_{90}	Range
S. aureus (all)	**ND**	**ND**	**ND**	**ND**	**8**	**≤0.06-->8**
S. aureus (MSSA)	≤0.06	0.016-->16	0.06	0.016--0.5	≤0.06	≤0.06--2
S. aureus (MRSA)	**ND**	**ND**	**ND**	**ND**	**>8**	**≤0.06-->8**
S. pneumoniae	1	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--1
E. coli	0.03	≤0.008--0.25	0.03	≤0.008--4	≤0.06	≤0.06--0.25
Klebsiella spp.	0.06	0.016-->16	0.06	0.016-->16	≤0.06	≤0.06-->8
Enterobacter spp.	0.12	≤0.008--4	0.12	0.016--2	0.12	≤0.06-->8
E. cloacae	ND	ND	0.12	0.016--1	0.12	≤0.06-->8
P. aeruginosa	**2**	**0.06-->16**	**4**	**0.016--16**	**4**	≤0.06-->8
Acinetobacter spp.	**2**	**0.06-->16**	**4**	**0.016--16**	**4**	≤0.06-->8
H. influenzae	0.25	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--0.5

MRSA, PA and AS have the highest DOR MIC values– 3 steps higher than next pathogen

Summary

- Analysis of DOR MIC increases:
  - DOR-09 (non-intubated): DOR MIC increases associated with clinical failure in DOR arm
  - DOR-10 (intubated): PA most common organism with ≥ 2 step increase; these were not necessarily clinical failures
  - MER MIC increases mirror doripenem increases
- Analysis of clinical failures: majority of patients had: polymicrobial infections, baseline MICs ≥ 1 MRSA infection, PA infection, or pathogens with ≥ 2 step increase in doripenem MIC on therapy

SUMMARY

- **Monte Carlo simulations:** probability of target attainment for PA and AS **below** range considered relevant to *in vivo* efficacy (> 90%)
- **Resistance studies**: serial passage studies—PA
  - 1. isolates treated with DOR alone had greater MIC increases than DOR + GM
  - 2. passage in DOR similar to MER, IMP
- ***In vitro***: multidrug-resistant CF isolates had elevated MIC90 values (32 mcg/ml mucoid, 64 mcg/ml non –mucoid); PA with metallo-beta-lactamases had MIC90 > 64 mcg/ml.
- **Surveillance Data**: doripenem has least activity against MRSA, *P. aeruginosa, or A. baumannii*