

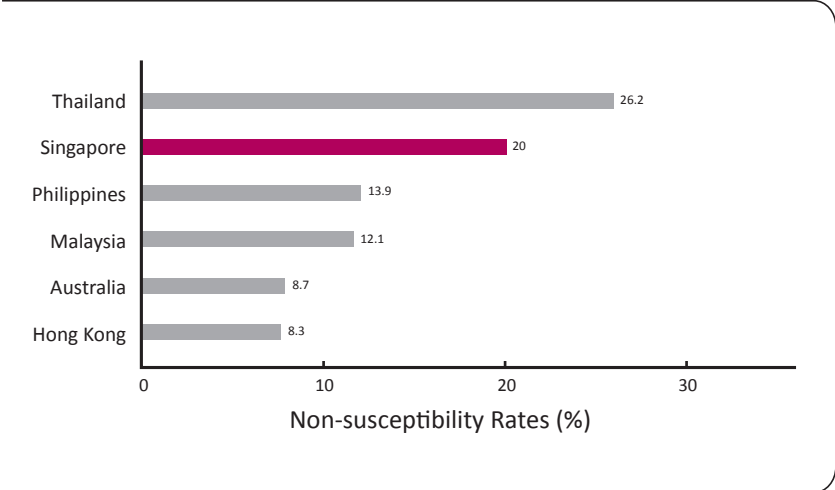
IN THEIR  
WEAKEST STATE  
THEY NEED  
THE STRONGEST  
DEFENCE



**DORIBAX™**  
doripenem for injection  
*TOUGH TO RESIST*

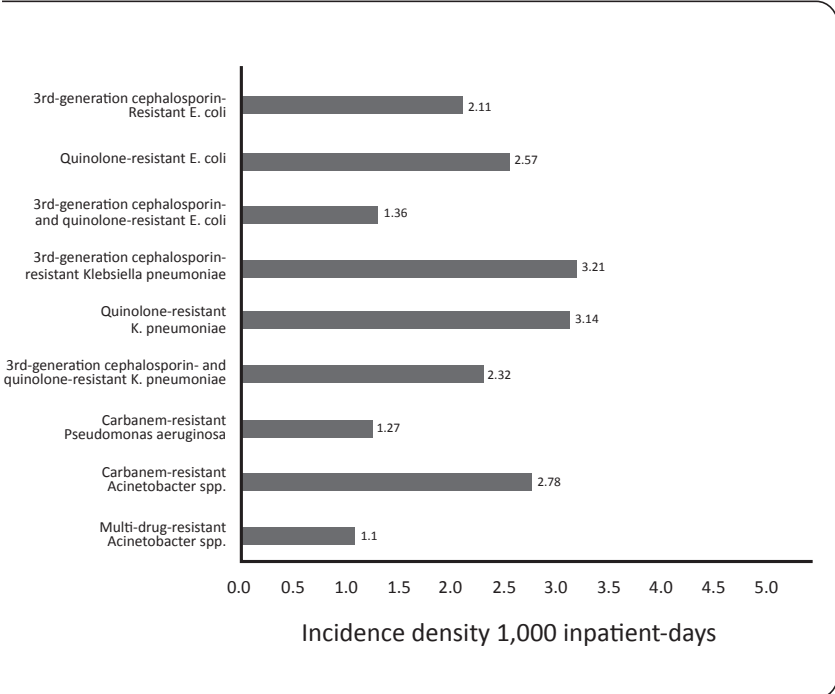
# Gram-Negative Resistance is a Growing Concern

## Antimicrobial drug resistance is a major problem in Singapore<sup>1</sup>



COMPACT AP Study – Comparative Activity of Carbapenem Testing evaluates in vitro activity of doripenem, imipenem and meropenem against selected Gram-negative, recent clinical isolates; *Pseudomonas aeruginosa*, Enterobacteriaceae, *Acinetobacter* and other gram-negative pathogens.<sup>2</sup>

## The issues of multi-drug resistant (MDR) pathogens in local ICUs are particularly pressing<sup>1</sup>



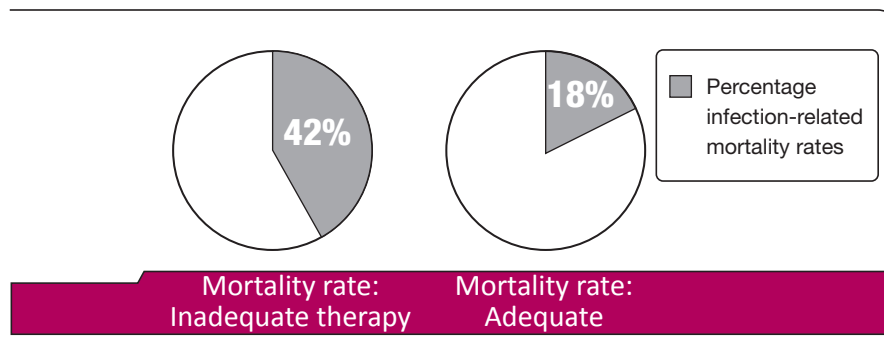
Incidence density, intensive-care unit (ICU) isolates (per 1,000 ICU inpatient-days) in public sector hospital Singapore 2006.<sup>1</sup>

NARSS – The Network for Antimicrobial Resistance Surveillance (Singapore)

# The Cost of Infections

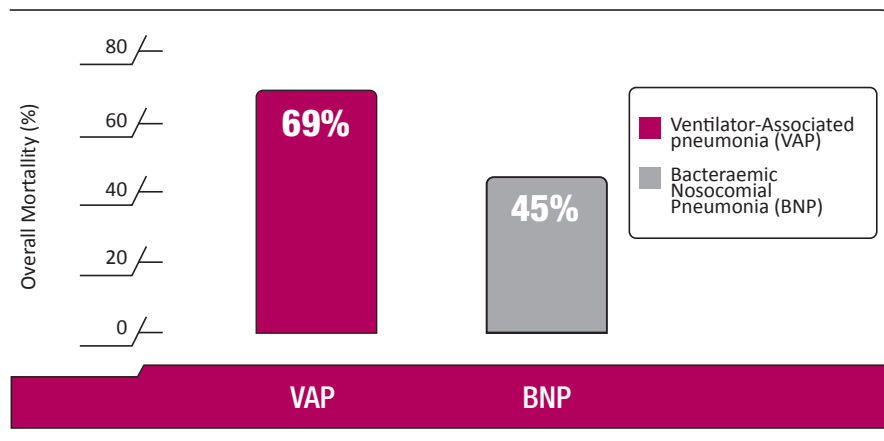
## Lives are being lost

➤ The infection-related mortality rate in ICU patients receiving inadequate antimicrobial treatment was 42% vs 18% in patients receiving adequate therapy.<sup>3</sup>

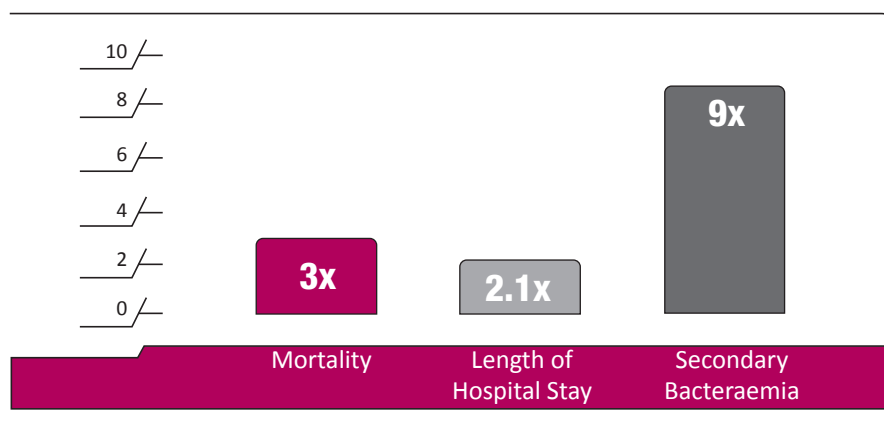


Data from a prospective cohort study of 2000 consecutive patients requiring admission to the medical or surgical ICU. Patients were segregated according to the presence or absence of inadequate antimicrobial treatment. Inadequate antimicrobial treatment was defined as failure to treat infections with antimicrobial agents, delays in the administration of antimicrobial therapy, or the initial use of agents to which the identified pathogens were resistant.<sup>2</sup>

➤ P.aeruginosa infection is associated with<sup>4</sup>:



➤ Emergence of resistant P.aeruginosa strains during therapy is associated with<sup>4</sup>:



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# What is Your Strategy?

## Get it right the first time

- Early aggressive therapy lowers mortality rates<sup>5</sup>

Traditional and new treatment paradigm

Traditional treatment paradigm	New treatment paradigm
Conservative start with 'workhorse antibiotics'	Hit hard and early with appropriate antibiotic(s)
↓	↓
Reserve more potent drugs for non-responders	Short treatment duration; de-escalate where possible

### Key principles of the new treatment paradigm

- Getting therapy right first time
- Use broad-spectrum antibiotics early
- Optimise antibiotic dosing and administration
- Base antimicrobial selection on knowledge of local susceptibility patterns
- Tailor or stop antibiotic therapy early and based on microbiological results (de-escalation)
- Give antibiotics for the correct duration

When treating serious infections empirically, choose the most potent agent in the class first...

### *...to improve outcomes today:*

- IDSA guidelines confirm that inadequate early antimicrobial therapy is associated with increased mortality in critically ill patients<sup>6</sup>

### *...to preserve essential agents tomorrow:*

- Initial therapy with less potent agents within a class increases the likelihood of cross-resistance and risks compromising the effectiveness of the class as a whole<sup>3</sup>
  - Less active members of a class are often more likely to select for resistance than their more active counterparts<sup>7</sup>

## Who are the Patients at Risk?

### Risk factors for multi-drug resistant pathogens<sup>8</sup>

Antibiotics in the preceding 90 d  
Hospitalization in preceding 90 d  
Current hospitalization  $5 \geq d$   
Duration of mechanical ventilation  $7 \geq d$   
History of regular visits to an infusion or dialysis center  
Residence in a nursing home or extended-care facility  
Immunosuppressive disease or therapy  
High frequency of antibiotic resistance in the community or ICU

- Pseudomonas is one of the common pathogens found in  $\geq 40\%$  of early onset VAP (occurring on or before day 5)
- Pseudomonas must be considered in any patient with one or more of the risk factors above, regardless of the duration of their hospitalization

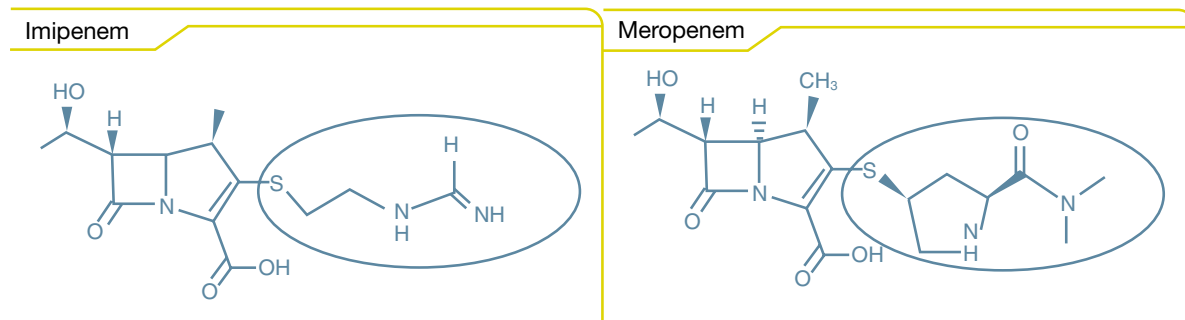
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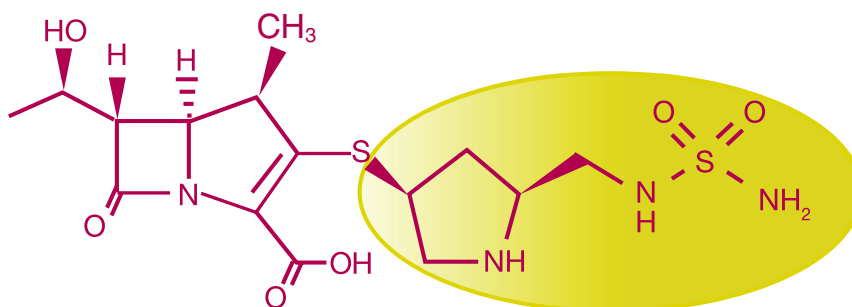
# Introducing DORIBAX™ – An Optimised Carbapenem

## A distinct molecular structure<sup>9</sup>

Carbapenem structures



## DORIBAX™



- Potency
  - Enhanced activity in vitro against *P.aeruginosa*<sup>9</sup>
- Safety
  - Lowest potential to induce seizures<sup>9,25</sup>
- Stability
  - Stable to Dehydropeptidase-1<sup>9</sup>
  - Highest stability after reconstitution with saline<sup>10</sup>
- Tough to resist
  - Lowest rate (in vitro) of emergence of resistant *P.aeruginosa*<sup>9</sup>
  - May preserve and prolong use of the entire carbapenem class<sup>9</sup>

# Broad-Spectrum Carbapenem Potency<sup>9,10,11,12</sup>

## Maintains potency vs ESBL containing pathogens

DORIBAX™ pathogen coverage in clinical infections

<b>AEROBES</b>	<b>Gram negative</b>	<i>Acinetobacter baumannii</i> *
		<i>Enterobacter cloacae</i>
		<i>Escherichia coli</i>
		<i>Klebsiella pneumoniae</i>
		<i>Haemophilus influenzae</i>
		<i>Proteus mirabilis</i>
		<i>Pseudomonas aeruginosa</i>
	<b>Gram positive</b>	<i>Staphylococcus aureus</i> (methicillin-susceptible)
		<i>Enterococcus faecalis</i> (vancomycin-susceptible)
		<i>Streptococcus pneumoniae</i>
		<i>Streptococcus pyogenes</i>
<b>ANAEROBES</b>	<b>Gram negative</b>	<i>Bacteroides caccae</i>
		<i>Bacteroides fragilis</i>
		<i>Bacteroides thetaiotaomicron</i>
		<i>Bacteroides uniformis</i>
		<i>Bacteroides vulgatus</i>
	<b>Gram positive</b>	<i>Peptostreptococcus micros</i>

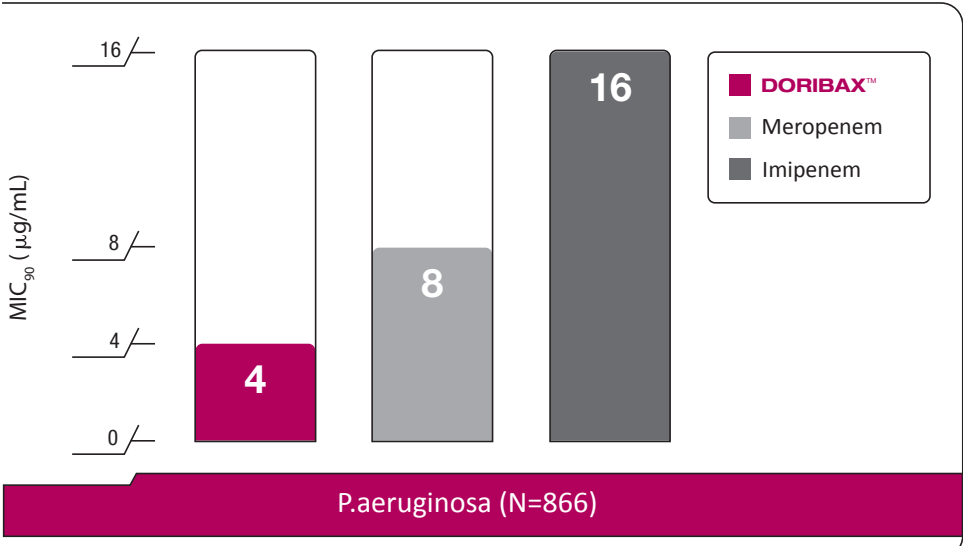
\* Active against carbapenemase negative strains

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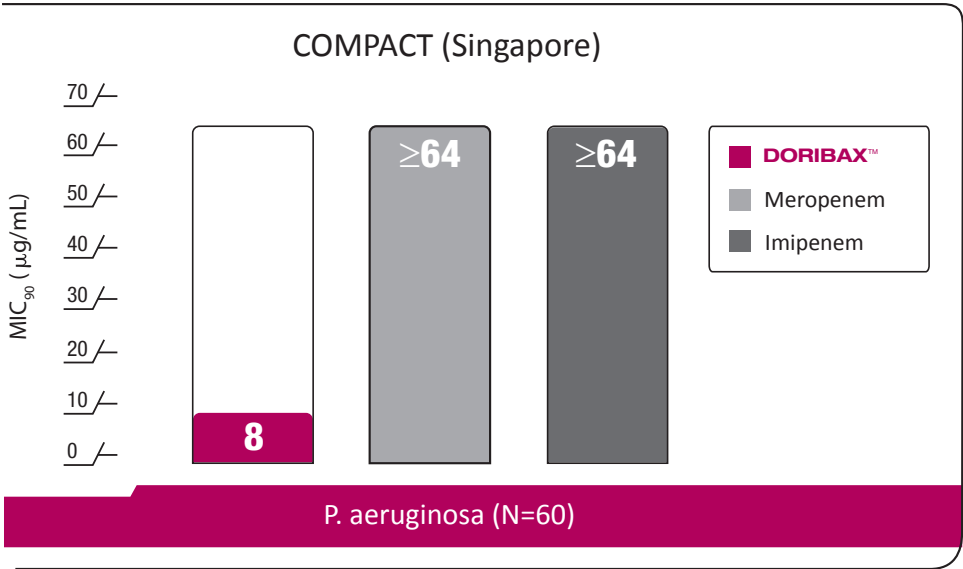
# Consistently More Potent Against P.aeruginosa Compared to Other Carbapenems

DORIBAX™ demonstrates 2-8 times lower MIC<sub>90</sub> vs P.aeruginosa<sup>2,13</sup>



In TRUST 11 (2007), gram-negative isolates, including P.aeruginosa (N=866), were collected from 45 US hospitals and tested against DORIBAX™ and several other antibacterials.<sup>13</sup>

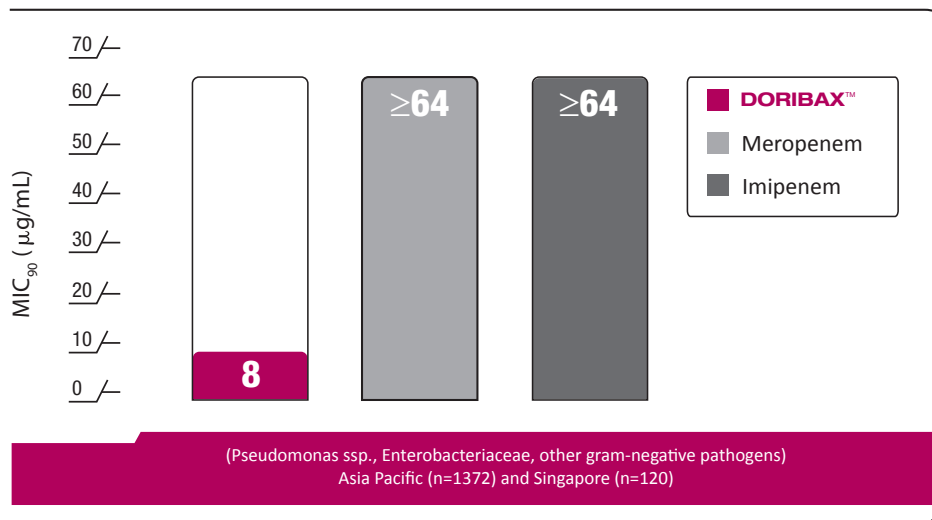
8



Compact AP Study - Comparative Activity of Carbapenem Testing Asia Pacific Study.<sup>2</sup>

# DORIBAX™ – Excellent MICs in Key Gram-Negative Pathogens<sup>2</sup>

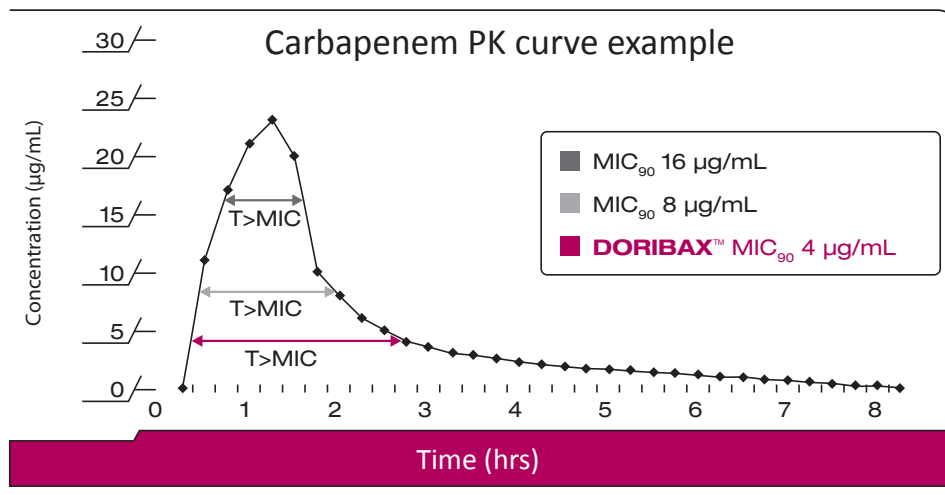
8 times better MICs than imipenem and meropenem<sup>2</sup>



Compact AP Study - Comparative Activity of Carbapenem Testing Asia Pacific Study.<sup>2</sup>

## DORIBAX™ - in vitro potency - lower MICs means enhanced killing

Lower MICs extend killing time vs P.aeruginosa<sup>14</sup>



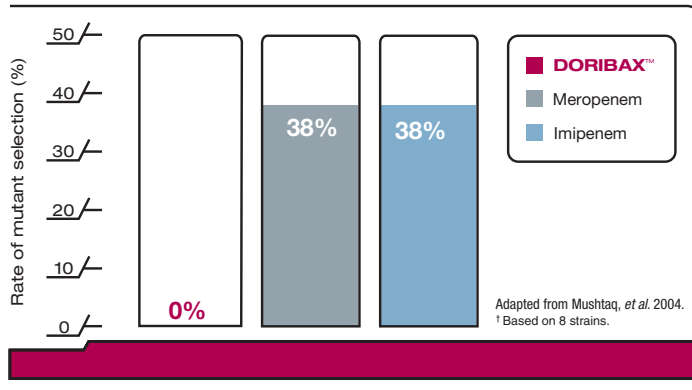
† Carbapenem PK profiles are similar when dosing is similar.  
‡ PK/PD data may not necessarily correlate with clinical results.

- Goal for time-dependent agents including carbapenems: maximize the duration of time that free drug levels exceed the MIC (%T>MIC)<sup>6</sup>
  - Lower MICs help extend the percentage of time above MIC<sup>15</sup>

## Lowest Potential to Select For Resistance<sup>9,16,17,18</sup>

Proven in 3 in vitro studies,

Propensity to select for resistant isolates at 8x MIC



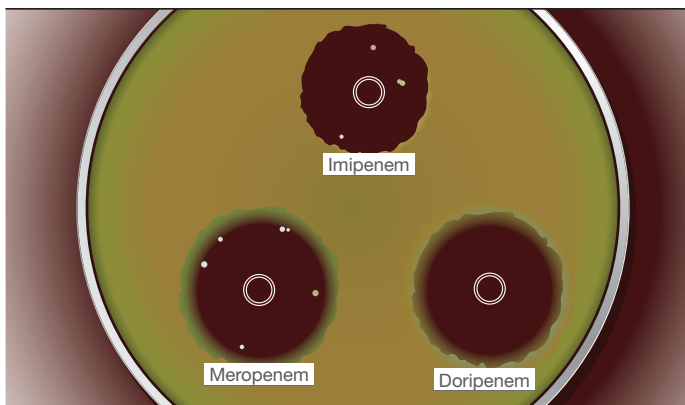
***“DORIBAX™ was less likely to select for resistant P.aeruginosa isolates in vitro.”***

—Mushtaq, et al, Antimicrobial Agents Chemotherapy 2004.<sup>16</sup>

***“The highest frequency of mutant cells was obtained in the presence of meropenem, while doripenem inhibited mutant growth.”***

—Tanimoto, et al, Antimicrobial Agents Chemotherapy 2008.<sup>17</sup>

Typical results: Colonies of carbapenem-resistant mutants within zones of growth inhibition<sup>18</sup>



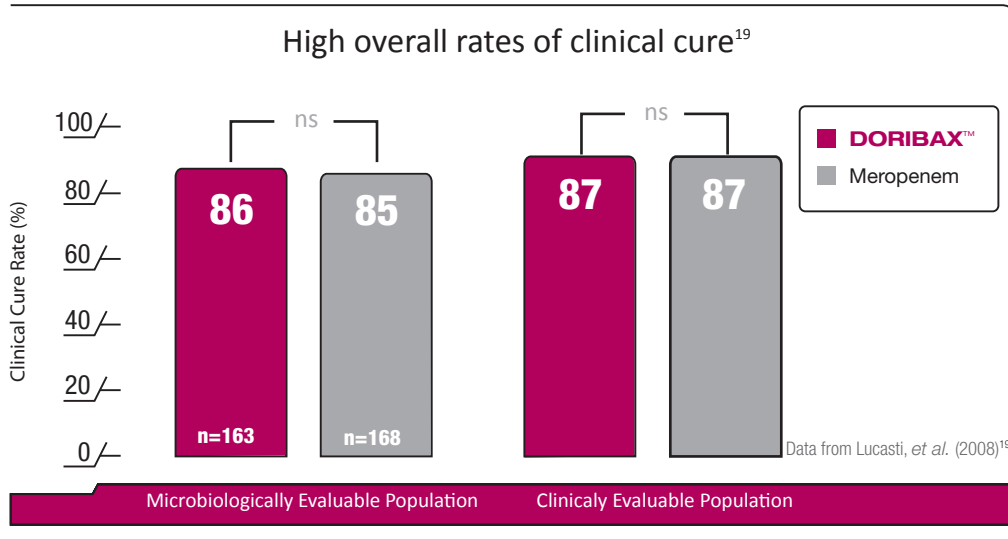
***“The results shown in this report indicated that [doripenem] exhibited the greatest ability to prevent the emergence of the mutant.”***

—Sakyo, et al, Journal of Antibiotics 2006<sup>18</sup>

➤ Doripenem exhibited both the lowest drug concentration and the narrowest range of drug concentration for selection of the carbapenem-resistant mutants.<sup>18</sup>

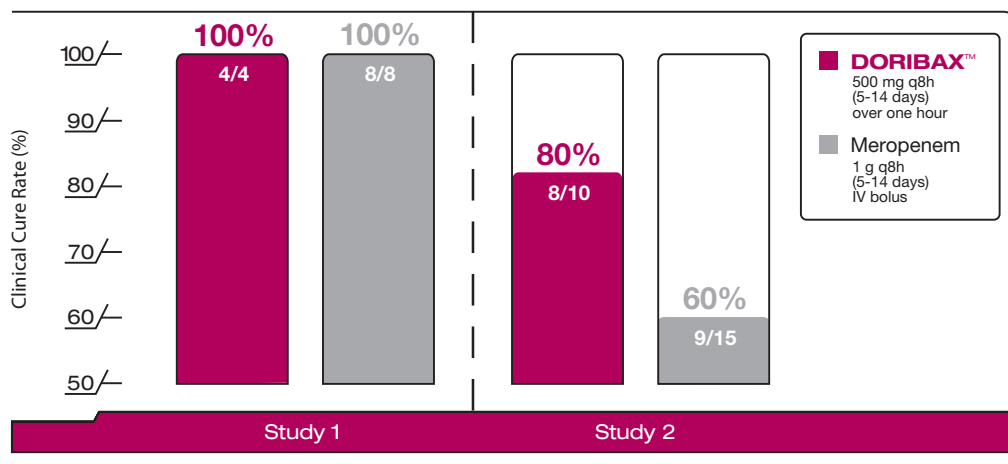
# DORIBAX™ – Clinical Efficacy in cIAI

Proven as effective as meropenem in 2 large Phase III (non-inferiority) clinical trials<sup>19</sup>



Subset analysis: DORIBAX™ proved clinically effective in bacteremia patients<sup>20</sup>

Clinical cure rates at TOC<sup>†</sup> (ME<sup>‡</sup> population) in patients with bacteraemia<sup>20</sup>



Two Phase III, multicenter, prospective, randomized, double-blind studies compared doripenem to meropenem in the treatment of complicated intra-abdominal infections (cIAI) in adults.

† TOC: Test of Cure Visit

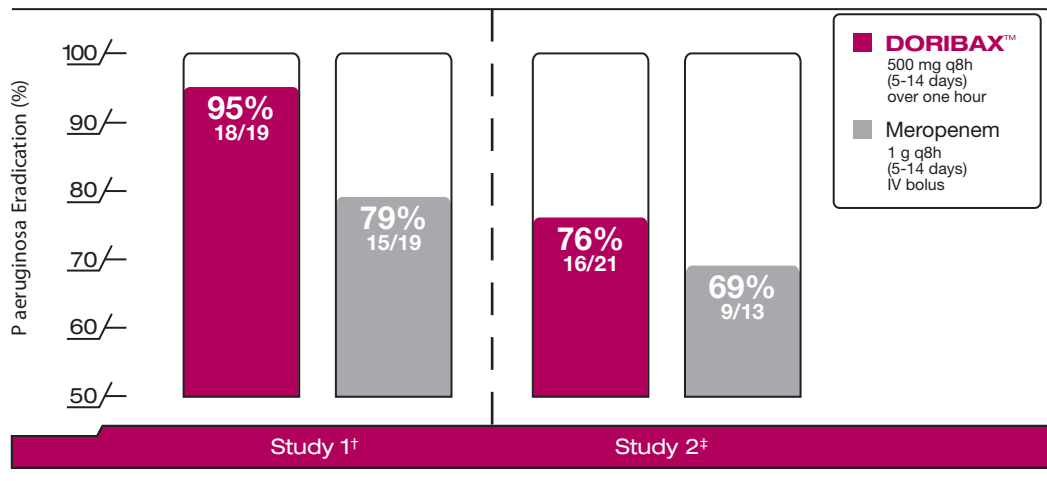
‡ ME: Microbiologically Evaluable Population

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# Excellent Pseudomonal and Gram-Negative Eradication in 2 cIAI Trials vs Comparator

Eradication rates against *P.aeruginosa* in cIAI (ME population)<sup>19,20</sup>



The cIAI trials (Study 1 and Study 2) were identical multicenter, prospective, randomized, double-blind studies comparing DORIBAX™ to meropenem. Treatment duration and dosing were the same in both trials.

<sup>†</sup> Study 1: 95% CI (-17.7%, 38.7%)

<sup>‡</sup> Study 2: 95% CI (-30.3%, 44.2%)

cIAI microbiological cure rates by gram-negative pathogen (ME population)<sup>§,19</sup>

Pathogen	DORIBAX™			Meropenem		
	N	n <sup>¶</sup>	%	N <sup>¶</sup>	n <sup>¶</sup>	%
<b>Aerobic</b>						
Enterobacteriaceae	157	140	89	141	122	87
<i>E coli</i>	104	91	88	100	84	84
<i>K pneumoniae</i>	15	14	93	9	9	100
Nonfermenters	23	22	96	24	17	71
<i>P aeruginosa</i>	19	18	95	19	15	79
<b>Anaerobic</b>	N	n <sup>¶</sup>	%	N <sup>¶</sup>	n <sup>¶</sup>	%
<i>B fragilis</i> group	75	67	89	89	75	84

§ = Favorable microbiological outcome with DORIBAX™ minus care with meropenem; not statistically different.

| N = number of unique baseline isolates.

¶ n = number of pathogens assessed as cured

# DORIBAX™ – Well-Tolerated

During clinical trials, adverse event rates have been similar to those associated with comparator agents<sup>10,19,21,22</sup>

Most common adverse drug reactions <sup>10</sup>				
	<b>DORIBAX™</b> (n=485)	<b>Imipenem</b> (n=263)	<b>DORIBAX™</b> (n=477)	<b>Meropenem</b> (n=469)
Diarrhoea	12%	17%	11%	11%
Nausea	7%	11%	12%	9%
Rash**	6%	6%	4%	2%
Headache	3%	3%	4%	5%
Increase in hepatic enzymes	3%	3%	1%	1%
Oral candidiasis	3%	2%	1%	2%
Phlebitis	2%	1%	8%	6%
Pruritis	1%	2%	3%	2%
Clostridium difficile colitis	1%	2%	< 1%	0%
Hypersensitivity	0%	0%	1%	< 1%
Vulvomycotic infection	0%	< 1%	1%	< 1%

\* Adverse drug reactions in this table include all those that occurred at a rate of  $\geq 1\%$  among doripenem-treated patients (i.e. during phase III clinical trials) and that were deemed to be related to the study drug.

\*\* Includes reactions reported as allergic and bullous dermatitis, erythema, macular/papular eruptions and erythema multiforme.

NOTE: Please refer to the DORIBAX™ Approved Product Information for a full list of all possible treatment-emergent adverse events, serious adverse events and adverse drug reactions, as well as Contraindications, Warnings and other Precautions.

## DORIBAX™ – Lowest Potential to Induce Seizures<sup>25</sup>

No reported seizures from treatment with DORIBAX™ during large Phase III clinical trials<sup>19,21,22</sup>

In the trial conducted by Chastre, *et al.* (2008), the overall rate of seizure was:<sup>21</sup>

- 1.1% in the DORIBAX™ group (3/262)
- 3.8% in the imipenem group (10/263)

>> All seizures in the DORIBAX™ group appeared unrelated to the study drug, as did all but one seizure in the imipenem group<sup>21</sup>

In the trial conducted by Réa-Neto, *et al.* (2008), the overall rate of seizure was:<sup>22</sup>

- 1.3% in the DORIBAX™ group (3/225)
- 2.7% in the piperacillin/tazobactam group (6/223)

>> All reported seizures occurred in patients with underlying risk factors and were not clearly related to either study drug<sup>22</sup>

### Minimal potential for CYP450 drug-drug interactions<sup>10</sup>

- DORIBAX™ does not inhibit or induce the major cytochrome P450 enzymes
- DORIBAX™ is not expected to inhibit or induce clearance of drugs metabolised by these enzymes to any clinically relevant extent

### DORIBAX™ is widely used<sup>23</sup>

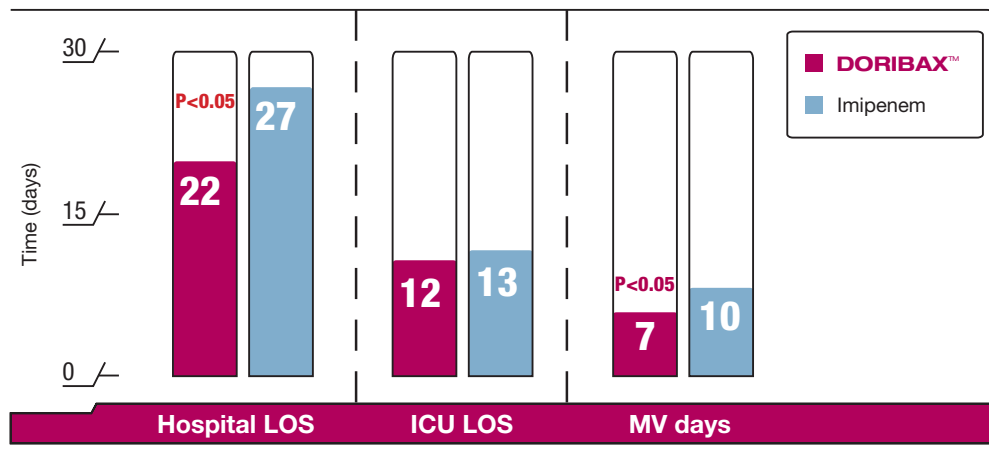
- Nearly 265,000 patients worldwide have been treated with DORIBAX™

# DORIBAX™ – Clinical and Economic Benefits

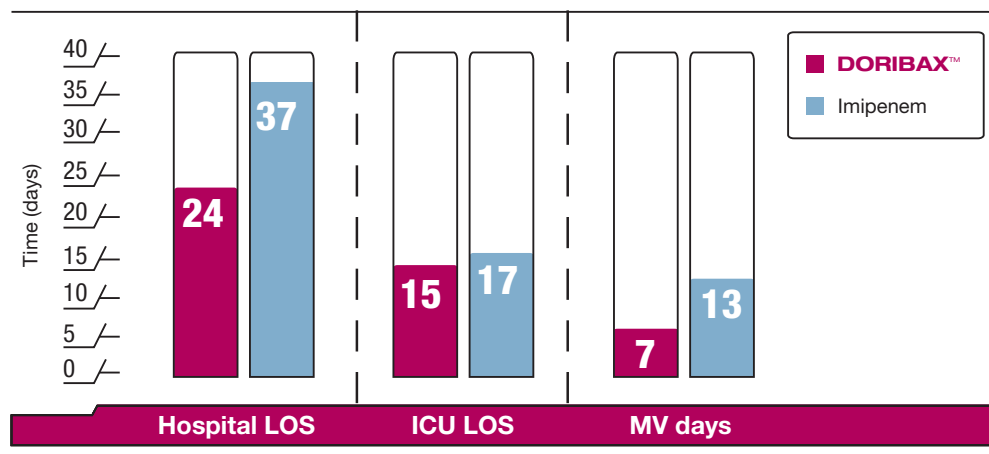
Median hospital length of stay (LOS) and mechanical ventilation (MV) was significantly shorter for DORIBAX™ vs comparator<sup>24</sup>

- 5 days shorter LOS
- 3 days shorter time on MV
- Cost savings of USD \$26,000/patient
- Lower risks of nosocomial infections
- Lower patient – patient bacteria transmission
- Positive patient outcomes

DORIBAX™ vs imipenem<sup>24</sup>



Patients with P.aeruginosa identified at baseline<sup>24</sup>



In patients with P.aeruginosa the magnitude of the differences between groups compared with overall sample warrants further study with a larger sample

# DORIBAX™ – Highly Stable

## Stability after reconstitution<sup>10</sup>

		Stability time	
Diluent	Infusion solution	Room temperature	2–8°C (Refrigeration)
Normal saline	DORIBAX™	12 hours	72 hours
	Imipenem <sup>^</sup>	4 hours	24 hours
	Meropenem <sup>^^</sup>	8 hours	24 hours
5% glucose*	DORIBAX™	4 hours	24 hours
	Imipenem <sup>^</sup>	4 hours	24 hours
	Meropenem <sup>^^</sup>	3 hours	14 hours

\* Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time, time to reach room temperature and infusion time does not exceed refrigeration stability time.  
 \* 5% glucose should not be used as diluent for infusions > 1 hour in duration.

<sup>^</sup> = Primaxin (imipenem) Prescribing Information.

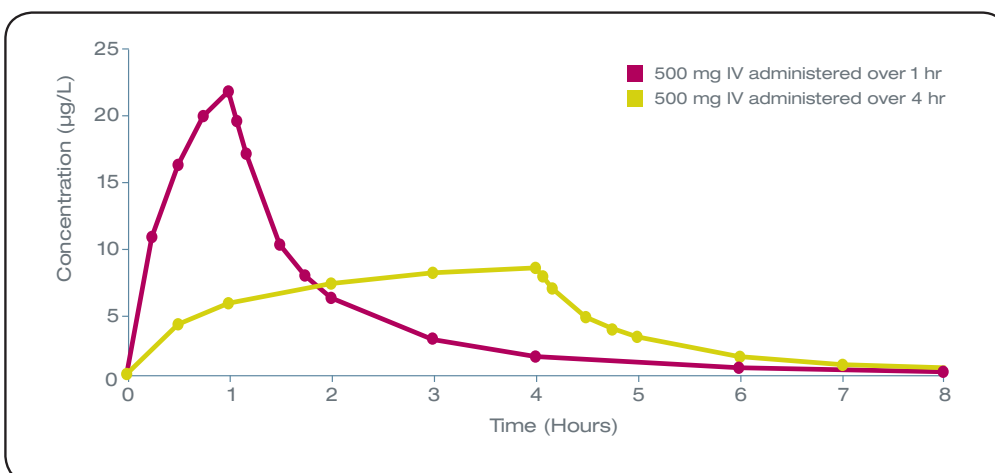
[http://www.merck.com/product/usa/pi\\_circulars/p/primaxin/primaxin\\_im\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/p/primaxin/primaxin_im_pi.pdf). Accessed October 9, 2008

<sup>^^</sup> = Merrem (meropenem) Prescribing Information.

<http://www.astrazeneca-us.com/pi/MerremIV.pdf>. Accessed October 9, 2008

## Favourable stability profile enables 4-hour infusion<sup>9</sup>

- Extending the infusion time to 4 hours helps to maximise  $T > MIC_{90}$  for a given dose, which may be crucial when targeting less susceptible pathogens<sup>10,21</sup>
- Favourable physicochemical stability may result in less product wastage, which may help to further minimise institutional costs



<sup>f</sup> 4-hourly infusion is an optional infusion time for NP/VAP patients who are at risk of infection by less susceptible pathogen; 5% glucose should not be used as diluent for infusions > 1 hour in duration.<sup>10</sup>

# DORIBAX™ – Simple Dosing

Recommended dosing for adult patients (≥ 18 years)<sup>10</sup>

Dosage of Doribax™ by infection				
Infection	Dosage	Frequency	Infusion time	Duration
cIAI	500 mg	q8h	1 hour	5–14 days*
cUTI, including pyelonephritis	500 mg	q8h	1 hour	10 days* <sup>§</sup>

\*Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.  
<sup>§</sup> Duration can be extended to up to 14 days for patients with concurrent bacteraemia.

Impaired renal function (all indications) <sup>#</sup>			
Estimated CrCl	Dosage	Frequency	Infusion time
> 50 mL/minute	No dose adjustment necessary		
≥ 30 to ≤ 50 mL/minute	250 mg	q8h	1 hour
> 10 to < 30 mL/minute	250 mg	q12h	1 hour

Note: DORIBAX™ is haemodialysable; however, there is insufficient information to make dose adjustment recommendations in patients on haemodialysis.

- NOTE:**
- No dose adjustment is required for elderly patients who have renal function that is normal for their age or for patients with impaired hepatic function<sup>#</sup>
  - A patient's body weight does not influence DORIBAX™ dosing<sup>#</sup>
  - DORIBAX™ does not have to be administered with a renal dehydropeptidase inhibitor, such as cilastatin<sup>#</sup>

## Consider DORIBAX™ – 1st Choice in Serious Infections...

### ...because :

- Gram Negative resistance is on the rise; of particular concern MDR pathogens in Singapore ---- increased mortality and costs<sup>1,4</sup>
- Inappropriate and inadequate antimicrobial therapy : 42% mortality vs 18% with adequate therapy<sup>3</sup>
- Early aggressive treatment lowers mortality<sup>5</sup>

### DORIBAX™ offers:

- Broad spectrum potency<sup>9,10,11,12</sup>
  - Effective against ESBL pathogens<sup>9</sup>
  - 2-8 times better MIC levels in key gram negative pathogens<sup>2</sup>
  - Consistently more potent (2-8 times lower MICs) against *P. aeruginosa* vs other carbapenems<sup>2,13</sup>
  - Low MICs extend killing time<sup>2,14</sup>
- Clinical efficacy proven in large phase III non-inferiority trials<sup>19,20,22</sup>
- Lowest potential to select for resistance<sup>9,16,17,18</sup>
- Lowest potential to induce seizures<sup>19,21,22,25</sup>
- Highest stability after reconstitution with saline<sup>10,21</sup>
  - Enables extended infusion times
  - Means longer T>MIC 90; crucial for less susceptible pathogens
- Significant reductions in hospital LOS, time on MV and cost<sup>14</sup>

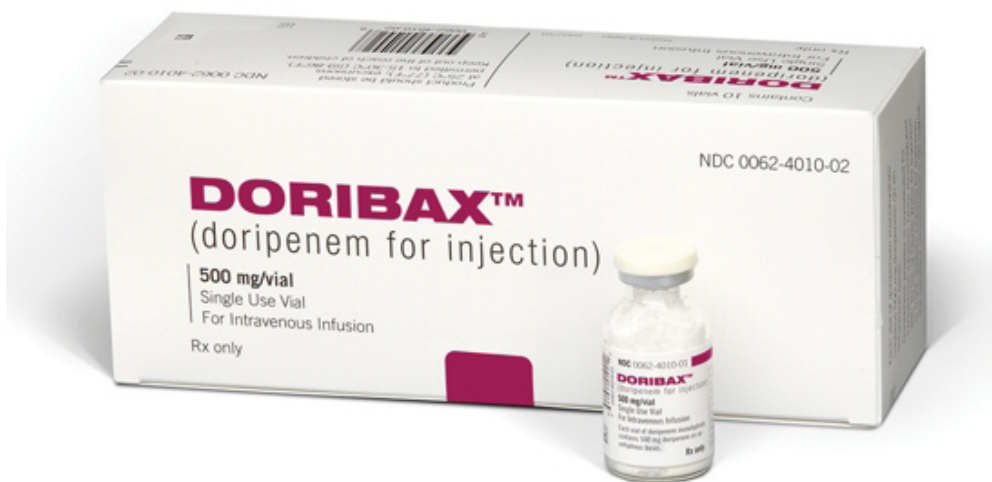
# DORIBAX™ – 1st Choice in Serious Infections...

...because :

*In their weakest state...*



*...their strongest defence is **YOU**...*



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**TOUGH TO RESIST**

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# A POTENT NEW FORCE TO TREAT GRAM-NEGATIVE INFECTIONS

[www.doribax.com](http://www.doribax.com)

Full prescribing information available upon request.  
For healthcare professionals.  
For more information, please email: [doribax.sg@its.jnj.com](mailto:doribax.sg@its.jnj.com)



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