Safety of Intravenous Infusion of Doripenem

Rebecca Redman and Thomas M. File, Jr.

Carbapenems remain a mainstay for the empirical treatment of serious nosocomial infection. Although the tolerance and safety profile of the carbapenems as a class is favorable, the primary safety concern is the potential for treatment-emergent seizures. In preclinical testing, doripenem, a new carbapenem antibiotic, showed negligible neurotoxic effects. The safety and tolerability of intravenous doripenem was evaluated in 1 phase 2 and in 6 phase 3 clinical trials conducted with patients with nosocomial pneumonia, including ventilator-associated pneumonia; complicated intra-abdominal infection; and complicated urinary tract infection. Safety data were available from 1817 patients who received doripenem and 1325 patients who received 1 of 4 active comparator drugs as part of this development program. Overall, intravenous doripenem was found to be safe and well tolerated, demonstrating a safety profile comparable to that of comparator agents and a limited propensity to induce seizures, including when administered via 1-h or 4-h infusion.

Carbapenems are a potent class of antimicrobial agents characterized by a broad spectrum of activity against a wide range of gram-positive and gram-negative organisms, especially multidrug-resistant gram-negative pathogens [1]. The carbapenems are recommended for empirical treatment of a variety of serious infections, because the overall rate of resistance of gram-negative bacterial pathogens to carbapenems is low and because carbapenems have a favorable safety profile [2]. As a result, their clinical use has increased during the past 2 decades as the prevalence of resistance to other classes of antibiotics has increased [2]. Doripenem, the newest member of the carbapenem family, which includes imipenem, meropenem, and ertapenem, is indicated for the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) in the United States as of October 2007. In addition to these indications, doripenem is also indicated for nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), in the European Union [3].

SAFETY OF CARBAPENEMS

Carbapenems, as a class, are generally safe and well tolerated. The most common adverse events associated with this antibiotic class, which are usually mild and self-limiting, include nausea, vomiting, diarrhea, rash, transient increases in liver enzyme concentrations, and infusion-site irritation [1]. More-serious adverse events, which occur infrequently, include allergic hypersensitivity reactions and seizures.

Hypersensitivity reactions. The potential for the development of allergic hypersensitivity is associated with the core β-lactam ring structure of the carbapenems. Although the incidence of hypersensitivity to carbapenems is low (<3% among the general population), carbapenems should be administered with caution to patients allergic to penicillin. Because the clinical features of penicillin allergy are highly varied and are determined by the type and severity of the reaction and the organ systems affected, the characteristics or details of a past allergic reaction must be weighed against the benefits of antibiotic use in each clinical situation. If a past reaction to penicillin involved an immediate, immunoglobulin E (IgE)–mediated reaction presenting with urticaria, angioedema, bronchospasm, or anaphy-
laxis, for example, more caution may be necessary in choosing the appropriate antibiotic than when the history involves a delayed reaction mediated by T cells, antibodies, or immune complexes [4].

In evaluations of the incidence of allergic cross-reactivity between carbapenems and penicillins, several studies have reported conflicting results [5–11]. One study examined the potential for IgE antibodies to penicillin determinants to cross-react with imipenem determinants in 40 patients with a history of allergic reaction to penicillin [5]. Of the 19 patients with a penicillin-positive skin test reaction to imipenem, 9 demonstrated a positive reaction during skin testing to nonirritating concentrations of imipenem and to several metabolized forms of the drug, indicating a cross-reactivity rate of 47.4%. Additional evidence of a potentially high rate of cross-reactivity between penicillins and the carbapenems was provided by 3 retrospective analyses of patients with reported penicillin allergies who had received systemic intravenous therapy with either imipenem-cilastatin or meropenem [6–8]. In these studies, ~10% of patients with a history of penicillin allergy, compared with 3%–4% of patients without a history of penicillin allergy, demonstrated a hypersensitivity reaction to imipenem-cilastatin or meropenem.

Recent studies in which penicillin-allergic patients were challenged with carbapenems concluded that cross-reactivity appeared to be infrequent and surmountable with graded challenges [9, 10]. In 1 prospective study, of the 112 patients with IgE-mediated allergy to various penicillins and a positive skin test reaction to penicillins, 1 patient had a positive skin test reaction to unmetabolized imipenem-cilastatin (0.9%) [9]. The patients who demonstrated a negative skin test reaction to imipenem-cilastatin underwent graded imipenem-cilastatin challenges during a 3-h period (1/100 of dose the first hour, 1/10 of dose the second hour, and the rest of the dose the third hour, all administered intramuscularly), with a total administered dose of 500 mg of imipenem, and no patient demonstrated a reaction. In a subsequent prospective study, of the 104 patients with IgE-mediated allergy to various penicillins and a positive skin test reaction to those agents, 1 patient had a positive skin test reaction to unmetabolized meropenem (0.9%) [10]. The other 103 patients tolerated a graded intravenous challenge to a normal dose of meropenem, which indicated a low rate of cross-reactivity between penicillins and meropenem. Because this challenge was not followed by a therapeutic course of the drug, reaction to treatment-level exposure is not known.

Neurotoxicity of carbapenems. In general, the primary safety concern associated with the use of carbapenems and other β-lactam antibiotic agents is treatment-emergent seizures. Clinical evidence suggests that the overall incidence of seizures among patients receiving carbapenem therapy is <2% [2]. The risk of seizure is increased in association with carbapenem use when the drug is given in higher doses or given to patients with renal dysfunction or central nervous system (CNS) disorder, which underscores the need for cautious use in at-risk populations.

Several studies have reported a higher seizure incidence when carbapenems are administered at high doses [1, 2, 11]. In an early clinical study that compared the utility of carbapenem monotherapy (1 g or 0.5 g of imipenem every 6 h) with that of a double β-lactam regimen (cefoperazone plus piperacillin or ceftazidime plus piperacillin) for patients with febrile granulocytopenia, the incidence of treatment-emergent seizures among patients who were given a high-dose imipenem regimen (1.0 g every 6 h) was 10% (3 of 29 patients), compared with 1% (1 of 106) among patients who received a low-dose imipenem regimen (0.5 g every 6 h) [12]. The patients who experienced treatment-emergent seizures during imipenem therapy had normal renal function and no history of seizures. Other predisposing risk factors for seizure during carbapenem therapy include decreased renal function and CNS abnormalities [1]. Patients with previous CNS injury (e.g., stroke and head injury) were more susceptible to treatment-related neurotoxic effects during carbapenem therapy than were patients without CNS injury [2].

In experimental animal studies conducted in the 1990s, carbapenems were reported to induce seizure discharges and to cause a lowering of the convulsive threshold induced by pentyleneetetrazol, a γ-aminobutyric acid (GABA)₃ receptor antagonist [13]. These preclinical findings suggest that the convulsive activity of the carbapenems may be attributable to the ability of β-lactams to block GABA-receptor binding, thereby inhibiting GABAergic neurotransmission. Down-regulation of GABAergic inhibitory signaling increases the risk of seizure by altering the balance between excitatory and inhibitory neurotransmission.

In a series of standard preclinical dose-response experiments, Horiuchi et al. [13] examined the potential convulsive activity of doripenem in various animal models and compared the seizure potential of doripenem with that of other β-lactams. In a murine model study, investigators evaluated the effects of intravenous (IV) administration of doripenem (100, 200, or 400 mg/kg), imipenem-cilastatin (100, 200, or 400 mg/kg), or meropenem (100, 200, or 400 mg/kg) on the behavior and electroencephalographic activity of rats. No electroencephalographic abnormalities or behavioral effects were observed in rats receiving doripenem at any dose. Although no electroencephalographic changes were observed with meropenem treatment, "wet dog" shakes occurred in several rats given doses of 200 or 400 mg/kg, suggesting some effect on the CNS. Rats given imipenem-cilastatin at a dose of ≥200/200 mg/kg demonstrated electroencephalographic spikes, and those given a
Figure 1. Effect of carbapenems on [3H]muscimol binding in mouse cerebral cortical membranes. The median inhibition concentration of competitors needed to inhibit 50% of the specific binding of [3H]muscimol (IC50) for doripenem was >10 mmol/L, the IC50 for meropenem was >10 mmol/L, the IC50 for imipenem was 0.48 mmol/L, and the IC50 for panipenem was 0.63 mmol/L. Data are from Horiuchi et al. [13].

The safety of doripenem (500 mg every 8 h via 1-h or 4-h infusion) was evaluated in 7 clinical trials comprising 6 phase 3 studies and 1 phase 2 study. The doripenem phase 2 or 3 trials were conducted with patients with NP, including VAP; cIAI; and cUTI. Safety data were available from a total of 1817 patients who received any dose or partial dose of doripenem with infections other than meningitis. Among patients with meningitis, the very low incidence of seizure was not considered to be drug related [14]. Similar to meropenem, ertapenem is considered to have a low potential to induce seizures [2]. Because ertapenem has a reduced spectrum of activity, its use is limited to treatment of serious community-acquired infections, and clinical data about its potential for causing seizures are limited [15]. Safety data from 7 published clinical trials indicate a seizure incidence of 0.18% among 1644 patients who received ertapenem [16]. In a recent case report, a patient who was undergoing peritoneal dialysis experienced 5 seizures after receiving 2 500-mg doses of IV ertapenem [16]. The possibility that the seizures were induced by ertapenem was validated with the Naranjo probability scale. The authors concluded that, because of the lack of clinical experience with this agent and the limited pharmacokinetic data in this patient population, ertapenem should be administered with caution to patients undergoing peritoneal dialysis.

Overall, these preclinical data suggest that doripenem may have a low potential for neurotoxic effects. Doripenem shows no ability to induce convulsions when given by IV or intracerebroventricular injection to experimental animals and, compared with other β-lactams, has a very low affinity for binding to the GABA_A receptor and for GABA inhibition.

ADVERSE DRUG REACTION PROFILE OF DORIPENEM

The safety of doripenem (500 mg every 8 h via 1-h or 4-h infusion) was evaluated in 7 clinical trials comprising 6 phase 3 studies and 1 phase 2 study. The doripenem phase 2 or 3 trials were conducted with patients with NP, including VAP; cIAI; and cUTI. Safety data were available from a total of 1817 patients who received any dose or partial dose of doripenem with infections other than meningitis. Among patients with meningitis, the very low incidence of seizure was not considered to be drug related [14]. Similar to meropenem, ertapenem is considered to have a low potential to induce seizures [2]. Because ertapenem has a reduced spectrum of activity, its use is limited to treatment of serious community-acquired infections, and clinical data about its potential for causing seizures are limited [15]. Safety data from 7 published clinical trials indicate a seizure incidence of 0.18% among 1644 patients who received ertapenem [16]. In a recent case report, a patient who was undergoing peritoneal dialysis experienced 5 seizures after receiving 2 500-mg doses of IV ertapenem [16]. The possibility that the seizures were induced by ertapenem was validated with the Naranjo probability scale. The authors concluded that, because of the lack of clinical experience with this agent and the limited pharmacokinetic data in this patient population, ertapenem should be administered with caution to patients undergoing peritoneal dialysis.

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(Ortho-McNeil-Janssen Pharmaceuticals, unpublished data). Of these patients, 1555 received doripenem at a dosage of 500 mg every 8 h via 1-h IV infusion and 262 received doripenem at a dosage of 500 mg every 8 h via 4-h IV infusion. Safety data were also available from a total of 1325 patients who received 1 of 4 active comparator drugs. Of these patients, 372 received levofloxacin (250 mg every 24 h via 1-h IV infusion), 469 received meropenem (1 g every 8 h via IV bolus injection over 3–5 min), 221 received piperacillin-tazobactam (4.5 g every 6 h via 30-min IV infusion), and 263 received imipenem (500 mg every 6 h via 30-min IV infusion or 1 g every 8 h via 1-h IV infusion). In 2 cUTI trials, 2 cIAI trials, and 1 NP trial, parenteral therapy with doripenem was followed by a switch to an oral antimicrobial agent.

Treatment-emergent adverse events (TEAEs) were defined as any adverse experiences that occurred or worsened during a patient’s participation in a clinical trial. TEAEs did not necessarily have a causal relationship with the study drug treatment. TEAEs with onset at or after the start of the first study drug infusion and within 30 days after administration of the last dose of study medication were reported. Study drug–related TEAEs were defined as any TEAE considered by the investigator to be possibly or probably related to the study drug.

Overall, the incidence of any study drug–related TEAE among patients who received doripenem was similar to that among patients who received an active comparator agent (table 1) (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data). The incidence of serious study drug–related TEAEs was generally low among patients who received doripenem and among patients who received a comparator agent. The rates of discontinuation due to study drug–related TEAEs were generally similar in both treatment groups. The percentage of patients in each treatment group who died was also similar. None of the TEAEs that culminated in death were considered by the investigator to be related to the study drug therapy.

Among patients who received doripenem, the occurrences of serious study drug–related TEAEs, discontinuation due to study drug–related TEAEs, and death were somewhat more common among those receiving doripenem via 4-h IV infusion than among those receiving doripenem via 1-h IV infusion. Doripenem was administered via 4-h IV infusion in 1 clinical trial involving only patients with VAP. Doripenem was administered via 1-h IV infusion to patients with NP (including early-onset VAP) and patients with cUTI and cIAI. The differences in rates of study drug–related TEAEs among patients who received doripenem may be largely attributable to differences in baseline clinical severity (clinical severity of VAP > clinical severity of NP > clinical severity of cUTI ≈ clinical severity of cIAI) between trial participants who received doripenem via 4-h IV infusion and those who received doripenem via 1-h IV infusion. Examination of the safety data obtained for patients with VAP reveals that both the regimen of doripenem at 500 mg every 8 h via 4-h IV infusion and the standard comparator regimen of imipenem were associated with comparable rates of serious study drug–related TEAEs (1.9% and 1.5%, respectively), discontinuation due to study drug–related TEAEs (3.1% and 2.7%), and death (13.4% and 12.2%). These findings suggest that a 4-h infusion of doripenem is associated with a safety and tolerability profile similar to that of imipenem administered by standard-length infusion.

Adverse drug reactions were TEAEs that the company assessed as being reasonably associated with the use of doripenem. The adverse drug reactions identified were headache, phlebitis, nausea, diarrhea, pruritis, rash, hepatic enzyme level increased, oral candidiasis, vulvomycotic infection, hypersensitivity reaction, and Clostridium difficile colitis (table 2) (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data).

**Neurotoxic effects.** The potential for seizures with carbapenem therapy is of particular importance in patients with known or previously unknown predisposing risk factors for seizures. Except for in the phase 3 cUTI trials in which levofloxacin was used as the comparator treatment and oral-switch agent, a history of seizures was not an exclusion criterion in the doripenem clinical trials. Patients with a known seizure

<table>
<thead>
<tr>
<th>Event</th>
<th>Doripenem</th>
<th>Comparator agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-h infusion (n = 1555)</td>
<td>4-h infusion* (n = 262)</td>
</tr>
<tr>
<td>Study drug–related TEAE**</td>
<td>402 (25.9)</td>
<td>45 (17.2)</td>
</tr>
<tr>
<td>Serious study drug–related TEAE**</td>
<td>2 (0.1)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Death</td>
<td>60 (3.9)</td>
<td>35 (13.4)</td>
</tr>
<tr>
<td>Discontinuation due to study drug–related TEAE**</td>
<td>13 (0.8)</td>
<td>8 (3.1)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients. Dosages were as follows: doripenem, 500 mg every 8 h via 1-h or 4-h infusion; levofloxacin, 250 mg every 24 h via 1-h infusion; meropenem, 1 g every 8 h via 3–5-min bolus injection; piperacillin-tazobactam, 4.5 g every 6 h via 30-min infusion; and imipenem, 500 mg every 6 h via 30-min infusion or 1 g every 8 h via 1-h infusion. Data are from Ortho-McNeil-Janssen Scientific Affairs.

* Clinical trial was conducted among patients with more-severe illness caused by ventilator-associated pneumonia.

** Includes possibly and probably related TEAEs and events with missing relationships.
disorder were allowed into the studies, provided their disorder was adequately controlled. In these trials, treatment-emergent seizures occurred in 6 (0.3%) of 1817 patients who received doripenem and in 17 (1.3%) of 1325 patients who received a comparator agent and was limited to or observed only in patients who received doripenem in the trials for NP-VAP (table 3) (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data).

In general, the risk of treatment-emergent seizures was significantly lower (by 70%) among patients who received doripenem than among those who received comparator agents (odds ratio, 0.3; 95% confidence interval, 0.1–0.7). Although the number of seizures observed was low in all treatment groups, no patient with cIAI who received either doripenem or meropenem had a seizure, and the difference in seizure rates between patients with V AP who received doripenem (1.1%) and those who received imipenem (3.8%) is consistent with preclinical data indicating that, compared with imipenem, doripenem has a limited propensity to induce seizures (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data).

Of the 6 patients given doripenem who had treatment-emergent seizures, 3 received a dosage of 500 mg every 8 h via 1-h IV infusion in the VAP trial and 3 received a dosage of 500 mg every 8 h via 4-h IV infusion in the VAP trial [17, 18]. No seizures were reported with doripenem at a dosage of 500 mg every 8 h via 1-h IV infusion in the 4 other phase 3 studies that included patients with cIAI and cUTI [17].

### Seizure in the NP trial.

Of the 3 patients who received doripenem at a dosage of 500 mg every 8 h via 1-h IV infusion in the NP trial, 1 had a history of hypertension and subarachnoid hemorrhage, 1 had a history of alcoholism and possible tremors from alcohol withdrawal, and 1 had a history of arterial hypertension and stroke complicated by right and left hemiplegia and seizures (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data). Of the 6 patients who received piperacillin-tazobactam (4.5 g every 6 h via 30-min infusion) in the same NP trial, 1 had a history of seizures, 1 had meningitis, and 3 had head or brain injuries. For 1 patient who had a seizure, the investigator believed that the episode was unlikely to be related to the study drug, because it did not recur during continued treatment with piperacillin-tazobactam (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data).

### Seizure in the VAP trial.

Of the 3 patients who received doripenem at a dosage of 500 mg every 8 h via 4-h IV infusion in the VAP trial, 2 had a subarachnoid hemorrhage and 1 had a history of epilepsy [18]. In comparison, of the 10 patients given imipenem in the VAP trial who had seizures, 5 received a dosage of 500 mg every 6 h. Of these 5 patients, 2 had head or brain injuries and 1 had a history of seizures. Of the other 5 patients who received imipenem at a dosage of 1 g every 8 h in the same trial and who also experienced seizures, 4 had head or brain injuries. Overall, 7 of 10 patients given the comparator agent imipenem in the VAP trial had a preexisting or underlying condition (head or brain injury or history of seizures) that predisposed them to seizures. A seizure was determined by the investigator to be related to the study drug in 1 patient who received imipenem [18].

### Seizures in previous studies.

In preclinical studies, doripenem had the lowest affinity among other tested carbapenems in binding to GABA receptors in vitro [13]. In animal studies, doripenem alone did not induce seizures, nor did it affect stimuli-induced seizures. Overall, as evidenced by data from in vitro, animal, and clinical studies, the potential for doripenem to induce seizures appears to be low [19].

Although the potential for seizures secondary to doripenem treatment appears to be minimal, it should be noted that the package insert for doripenem in both Japan and the United

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### Table 2. Adverse drug reactions in phase 2 and 3 clinical trials of doripenem.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Doripenem (n = 1817)</th>
<th>Levofloxacin (n = 372)</th>
<th>Meropenem (n = 469)</th>
<th>Piperacillin-tazobactam (n = 221)</th>
<th>Imipenem (n = 263)</th>
<th>Comparator agents combined (n = 1325)</th>
<th>OR (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium difficile infection</td>
<td>9 (0.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (0.9)</td>
<td>6 (2.3)</td>
<td>8 (0.6)</td>
<td>0.8 (0.3–2.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>163 (9.0)</td>
<td>38 (10.2)</td>
<td>52 (11.1)</td>
<td>24 (10.9)</td>
<td>45 (17.1)</td>
<td>159 (12.0)</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>183 (10.1)</td>
<td>54 (14.5)</td>
<td>24 (5.1)</td>
<td>5 (2.3)</td>
<td>8 (3.0)</td>
<td>91 (6.9)</td>
<td>1.5 (1.2–2.0)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>12 (0.7)</td>
<td>3 (0.8)</td>
<td>2 (0.4)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>6 (0.5)</td>
<td>1.5 (0.5–4.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>142 (7.8)</td>
<td>22 (5.9)</td>
<td>44 (9.4)</td>
<td>7 (3.2)</td>
<td>28 (10.6)</td>
<td>101 (7.6)</td>
<td>1.0 (0.8–1.4)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>23 (1.3)</td>
<td>0 (0)</td>
<td>8 (1.7)</td>
<td>1 (0.5)</td>
<td>6 (2.3)</td>
<td>15 (1.1)</td>
<td>1.1 (0.6–2.3)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>103 (5.7)</td>
<td>15 (4.0)</td>
<td>26 (5.5)</td>
<td>5 (2.3)</td>
<td>2 (0.8)</td>
<td>48 (3.6)</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>33 (1.8)</td>
<td>4 (1.1)</td>
<td>9 (1.9)</td>
<td>1 (0.5)</td>
<td>5 (1.9)</td>
<td>19 (1.4)</td>
<td>1.3 (0.7–2.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>67 (3.7)</td>
<td>3 (0.8)</td>
<td>11 (2.3)</td>
<td>7 (3.2)</td>
<td>16 (6.1)</td>
<td>37 (2.8)</td>
<td>1.3 (0.9–2.1)</td>
</tr>
<tr>
<td>Vulvomycotic infection</td>
<td>14 (0.8)</td>
<td>4 (1.1)</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>7 (0.5)</td>
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a Pairwise comparison for doripenem vs. comparators combined, by exact estimate of OR.
States lists seizures as a possible TEAE. Because carbapenems have, as a class, been linked to seizure-causing effects, good clinical practice dictates that doripenem be administered with caution to patients who may, because of a comorbid medical condition (e.g., CNS injury or renal impairment), be at increased risk for the development of seizures.

C. difficile infection. C. difficile infection has been identified as a serious and potentially fatal adverse effect of virtually all antibacterial agents; the association between antibacterial therapy and C. difficile infection has been attributed to the ability of antibacterial agents to alter the normal flora of the colon in a manner that allows overgrowth of C. difficile. In clinical testing of doripenem, the rates of study drug–related C. difficile infection were low among patients who received doripenem (0.3% [5 of 1817 patients]) and patients who received a comparator agent (0.2% [3 of 1325]). In addition, the odds of developing study drug–related C. difficile infection in either treatment group did not differ significantly (odds ratio, 1.2; 95% confidence interval, 0.2–7.8) (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data).

Liver enzyme abnormalities. Patients met criteria for Hy’s high-risk classification if they had an alanine aminotransferase (ALT) level >3 times the upper limit of normal and a bilirubin level >1.5 times the upper limit of normal, unless they had a concurrent alkaline phosphatase level >1.5 times the upper limit of normal. The percentage of patients who were classified as at Hy’s high risk in the doripenem treatment groups (500 mg by 1-h or 4-h infusion) was very low (0.8%) and was within the range of percentages for the comparator treatment groups: meropenem, 0.4%; piperacillin-tazobactam, 1.3%; imipenem, 3.8%; and levofloxacin, 0%. Evaluation of patients revealed that all had underlying medical conditions that confounded interpretation of the relatedness of the hepatic dysfunction (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data) [20].

An increased hepatic enzyme level was documented as a study drug–related adverse event for 1.1% of patients (16 of 1817) who received doripenem and 1.1% of patients (11 of 1325) given a comparator agent; the difference between the 2 treatment groups was not statistically significant (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data). Patients were considered to meet the classification of hepatic enzyme increase if they had an ALT or aspartate aminotransferase (AST) level that was less than or equal to the upper limit of normal at baseline and >5 times the upper limit of normal at the end of IV treatment. This determination of increased hepatic enzyme levels was calculated from laboratory data to approximate a standardized definition of clinical relevance.

In the pooled safety data analysis, study drug–related abnormal liver function test results were reported as adverse events for 2 (0.1%) of 1817 patients who received doripenem and 4 (1.5%) of 263 patients who received imipenem. The patients identified with abnormal liver function test results were participants in the VAP clinical trial, and this finding may be attributable to the greater severity of illness in the intensive care unit population enrolled in that trial. Abnormal liver function test results were not reported for patients in the levofloxacin, meropenem, or piperacillin-tazobactam treatment groups.

Among all treatment groups, the mean ALT, AST, γ-glutamyl transference, and alkaline phosphatase levels generally increased from baseline to the end of IV treatment and then returned to near baseline or below baseline levels by a late follow-up visit (28–35 days after completion of the study treatment). The exceptions were the ALT and AST levels in the imipenem treatment group, which decreased from baseline through follow-up, and the alkaline phosphatase level in the imipenem treatment group, which increased from baseline to the end of IV treatment and continued to increase from the end of IV treatment through follow-up.

The mean total bilirubin levels decreased from baseline to the end of IV treatment in all treatment groups, continued to

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<tbody>
<tr>
<td>Any seizure event</td>
<td>6 (0.3)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>6 (2.7)</td>
<td>10 (3.8)</td>
<td>17 (1.3)</td>
<td>0.3 (0.1–0.7)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>5 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (2.3)</td>
<td>7 (2.7)</td>
<td>12 (0.9)</td>
<td>0.3 (0.1–0.9)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>2 (0.8)</td>
<td>3 (0.2)</td>
<td>0.2 (0.0–3.0)</td>
</tr>
<tr>
<td>Grand mal convulsion</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>0.0 (0.0–13.9)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>1 (0.1)</td>
<td>0.0 (0.0–13.9)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise specified. Dosages were as follows: doripenem, 500 mg every 8 h via 1-h or 4-h infusion; levofloxacin, 250 mg every 24 h via 1-h infusion; meropenem, 1 g every 8 h via 3–5 min bolus injection; piperacillin-tazobactam, 4.5 g every 6 h via 30-min infusion; and imipenem, 500 mg every 6 h via 30-min infusion or 1 g every 8 h via 1-h infusion. Patients from the phase 2 trial who received doripenem at a dosage of 250 mg are not included in the calculations. At each level of summarization, a patient was counted once if the patient reported ≥1 event. Seizures were adverse events designated with the Medical Dictionary for Regulatory Activities high-level group term of “seizures (including subtypes).” Seizure events were reported for the subtypes convulsion, epilepsy, grand mal convulsion, and status epilepticus only. CI, confidence interval; OR, odds ratio. Data are from Ortho-McNeil-Janssen Scientific Affairs.

a OR for doripenem vs. comparators combined.

Table 3. Treatment-emergent seizures in doripenem clinical trials.

The mean total bilirubin levels decreased from baseline to the end of IV treatment in all treatment groups, continued to
decrease through follow-up in the doripenem, piperacillin-tazobactam, and imipenem treatment groups, and increased slightly in the levofloxacin and meropenem treatment groups. Shifts in hepatobiliary values from normal at baseline (grade 0) to grade 4 were rare for all analyzed groups. Although clinically significant increases in liver enzyme concentrations were rarely seen in individual patients, carbapenems have been associated with liver function abnormalities, and for at least 1 patient among the pooled patient population, the company assessed the liver enzyme level increase as possibly related to doripenem therapy (Ortho-McNeil-Janssen Pharmaceuticals, unpublished data).

SAFETY OF DORIPENEM IN THE TREATMENT OF NP

Adverse events experienced by patients with NP were considered separately, because these patients tend to have a higher severity of illness and, thus, require a separate risk-to-benefit assessment. The first phase 3 study, reported by Réa-Neto et al. [17], was a randomized, open-label, prospective study that enrolled patients who met clinical and radiological criteria for NP and who, at baseline, were not receiving mechanical ventilation (i.e., had non–ventilator-associated NP) or had been receiving mechanical ventilation for ≤5 days (i.e., had early-onset VAP). Trial participants were randomly assigned in a 1:1 ratio to receive either doripenem (500 mg every 8 h via 1-h IV infusion) or piperacillin-tazobactam (4.5 g every 6 h via 0.5-h IV infusion). Patients were to receive the study treatment for a minimum of 7 days and a maximum of 14 days. Vancomycin was added to the treatment regimen at the discretion of the investigator if there was suspicion of infection due to methicillin-resistant Staphylococcus aureus. Because the addition of an aminoglycoside is recommended with piperacillin-tazobactam therapy for patients at risk of Pseudomonas aeruginosa infection [21], amikacin was recommended in both treatment arms, to ensure balance. The second phase 3 trial, reported by Chastre et al. [18], was a randomized, open-label, prospective study that enrolled patients who met clinical and radiological criteria for VAP (early onset or late onset) and who had a Clinical Pulmonary Infection Score ≥5, as classified by the Luna scoring method. Trial participants were randomly assigned in a 1:1 ratio to receive either doripenem (500 mg every 8 h via 4-h IV infusion) or imipenem (500 mg every 6 h via 0.5-h IV infusion or 1000 mg every 8 h via 1-h IV infusion, depending on the standard practice at the center where treatment was administered). In this study, patients were to receive the study treatment for a minimum of 7 days and a maximum of 14 days. Vancomycin, amikacin (or another aminoglycoside), or both were added to the treatment regimen at the discretion of the investigator if there was suspicion of infection with methicillin-resistant S. aureus, P. aeruginosa, or both, respectively.

In the NP study, in which 500 mg of doripenem was administered every 8 h via 1-h IV infusion (n = 223), the most common TEAEs occurring in the doripenem treatment arm that were considered by the investigator to be related to study drug were an elevated γ-glutamyl transferase level (6 patients [2.7%]), thrombocytopenia (4 [1.8%]), diarrhea (4 [1.8%]), an elevated ALT level (4 [1.8%]), an elevated AST level (3 [1.3%]), an increased eosinophil count (3 [1.3%]), and phlebitis (3 [1.3%]) [17]. The incidence of these events among patients who received piperacillin-tazobactam (n = 221) was generally similar; elevation in γ-glutamyl transferase level occurred in 4 patients (1.8%), thrombocytopenia in 5 (2.3%), diarrhea in 5 (2.3%), elevated ALT level in 2 (0.9%), elevated AST level in 1 (0.5%), increased eosinophil count in 1 patient (0.5%), and phlebitis in 2 (0.9%).

In the VAP study, in which 500 mg of doripenem was administered every 8 h via 4-h IV infusion (n = 262), the most commonly occurring related TEAEs included an elevated hepatic enzyme level (12 patients [4.6%]), diarrhea (5 [1.9%]), rash (5 [1.9%]), vomiting (4 [1.5%]), nausea (3 [1.1%]), fungal infection (3 [1.1%]), and abnormal liver function test results (2 [0.8%]) [18]. The incidence of these events among patients who received imipenem (n = 263) was similar; an elevated hepatic enzyme level occurred in 6 patients (2.3%), diarrhea in 8 (3.0%), rash in 2 (0.8%), vomiting in 2 (0.8%), nausea in 6 (2.3%), fungal infection in 1 (0.4%), and abnormal liver function test results in 4 (1.5%). The higher rates of adverse events reported among the patients receiving doripenem via 4-h infusion may be related to the patient population under study and not necessarily to the longer infusion time.

CONCLUSION

Overall, IV doripenem is generally safe and well-tolerated. Data from preclinical testing suggest that doripenem may have less seizure potential than other carbapenems. Doripenem showed minimal potential for seizures or convulsions when administered by IV or intracerebroventricular injection to experimental animals. Compared with other β-lactams, doripenem showed a low affinity for binding to the GABA receptor in vitro. Available clinical trial data suggest that the overall adverse event profile of doripenem is similar to that of other commonly used antimicrobial agents, including other carbapenems. Data from prospective clinical trials also mirror preclinical findings and suggest that the risk of seizure in patients who take doripenem is low, but additional clinical surveillance data will be needed to further characterize the risk in a broad population of treated patients. To date, the minimal convulsant activity shown in both preclinical and clinical studies suggests the potential for safe administration of even higher doses of doripenem to patients with particularly challenging infections. In the vulnerable population of patients with NP, doripenem has a safety and
tolerability profile similar to that of other antibiotic agents, including carbapenems.

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