DORIBAX 500 mg, powder for solution for perfusion
B/10 bottles (CIP: 387 355-6)

Applicant: JANSSEN-CILAG
doripenem
ATC code: J01DH04
List I
Medicinal product for hospital prescription only

Date of Marketing Authorisation: 25 July 2008 (centralised procedure)

Reason for request: Inclusion on the list of medicines approved for use by hospitals.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
doripenem

1.2. Background
Doripenem is a new beta-lactam antibiotic, which belongs to the carbapenem class.

1.3. Indications
“Doribax is indicated for the treatment of the following infections in adults:
- Nosocomial pneumonia (including ventilator–associated pneumonia)
- Complicated abdominal infections
- Complicated urinary tract infections

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

1.4. Dosage
The recommended dosage and administration by infection is shown in the following table:

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dose</th>
<th>Frequency</th>
<th>Perfusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial pneumonia including ventilator–</td>
<td>500 mg</td>
<td>every 8 hours</td>
<td>1 or 4 hours*</td>
</tr>
<tr>
<td>associated pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated abdominal infections</td>
<td>500 mg</td>
<td>every 8 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td>Complicated UTI, including pyelonephritis</td>
<td>500 mg</td>
<td>every 8 hours</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

*Based mainly on PK/PD considerations, a 4-hour perfusion time may be more suitable for infection with less susceptible pathogens (see section 5.1 of the SPC). This dosing regimen should also be considered in particularly severe infections.

The usual treatment duration of doripenem therapy is 5-14 days and should be guided by the severity, site of the infection and the patient's clinical response. Doripenem was given for up to 14 days in clinical studies and the safety of longer durations of therapy has not been established. After starting treatment with intravenous doripenem, a switch to appropriate oral therapy to complete the treatment course is possible once clinical improvement has been established.

Dosage in paediatric patients
Doribax is not recommended for use in children below 18 years of age due to a lack of safety and efficacy data.

Dosage in patients with impaired renal function
In patients with mild renal failure (i.e. creatinine clearance (CrCl) is 51-79 ml/min), no dosage adjustment is necessary. In patients with moderate renal failure (CrCl 30 to < 50 ml/min), the dosage of Doribax should be 250mg every 8 hours. In patients with severe renal failure (CrCl < 30ml/min), the dosage of Doribax should be 250mg every 12 hours. Due to limited clinical data and an expected increased exposure of doripenem and its metabolite, Doribax should be used with caution in patients with severe renal failure (see section 5.2 of the SPC).

Dosage in patients on dialysis
Doribax is haemodialysable; however, there is insufficient information to make dose adjustment recommendations in patients on dialysis. Therefore, Doribax is not recommended for patients on dialysis (see section 5.2 of the SPC).

Dosage in elderly patients (≥ 65 years of age)
No dosage adjustment is necessary in elderly patients, except in cases of moderate to severe renal insufficiency (see Dosage in patients with impaired renal function, above, and section 5.2 of the SPC).

Dosage in patients with impaired hepatic function
No dosage adjustment is necessary.
Method of administration
Doribax has to be reconstituted and then further diluted (see section 6.6) prior to administration by intravenous perfusion over a period of one or four hours.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)
J: Antiinfectives for systemic use
J01: Antibacterials for systemic use
J01D: Other beta-lactam antibacterials
J01DH: Carbapenems
J01DH04: doripenem

2.2. Medicines in the same therapeutic category
2.2.1. Comparator medicines
Medicines in the carbapenem class

<table>
<thead>
<tr>
<th>INN</th>
<th>Proprietary product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem-</td>
<td>TIENTAM</td>
<td>Limited to severe infections caused by micro-organisms that are sensitive to imipenem, particularly of the following types: abdominal; broncho-pulmonary; gynaecological; sepsicaemia; genito-urinary; bone and joint; skin and soft tissue; endocarditis; with the exception of meningitis.</td>
</tr>
<tr>
<td>cilastatin</td>
<td>powder intravenous perfusion solution</td>
<td></td>
</tr>
<tr>
<td>Marketing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>authorisation</td>
<td>1986</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>MERONEM</td>
<td>Limited to severe infections, whether bacteraemia or not, caused by meropenem-sensitive micro-organisms in the following indications: lower respiratory infections; abdominal infections; febrile episodes in neutropenic patients</td>
</tr>
<tr>
<td>Marketing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>authorisation</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Amended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>marketing</td>
<td>18/02/2008</td>
<td></td>
</tr>
<tr>
<td>authorisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>INVANZ</td>
<td>Treatment of the following infections when they are caused by strains of bacteria that are known to be sensitive or possibly sensitive to ertapenem and when parenteral treatment is required: - Abdominal infections; - Community-acquired pneumonia; - Acute gynaecological infections; - Infections of skin and soft tissue of feet in patients with diabetes</td>
</tr>
<tr>
<td>Marketing</td>
<td>Powder intravenous perfusion solution</td>
<td></td>
</tr>
<tr>
<td>authorisation</td>
<td>2002</td>
<td></td>
</tr>
</tbody>
</table>

2.3. Medicines with a similar therapeutic aim
All antibiotics with the same spectrum of anti-microbial activity or with similar spectra, administered parenterally.
3.1. Efficacy

3.1.1. Nosocomial pneumonia

The clinical development program is based on two controlled studies, the aim of which was to demonstrate non-inferiority (delta threshold = 20%) of doripenem (DORIBAX) to piperacillin/tazobactam (study DORI-09)\(^1\) and to imipenem/cilastatin (study DORI-10)\(^2\).

**Study features**

**Populations**

The patient inclusion and non-inclusion criteria were similar in the two studies, with the exception of the severity of the disease involved:

- **DORI-09 study**: adult patients with nosocomial pneumonia, admitted to hospital at least 48 hours ago, or discharged from a hospital admission lasting at least 48 hours within the last 7 days, during which they were non-ventilated or ventilated for less than 5 days.
- **DORI-10 study**: adult patients with ventilation pneumonia, on mechanical ventilation for more than 24 hours or weaned from ventilation within the last 72 hours, with a clinical pulmonary infection score (CPIS) of > 5, requiring intravenous treatment.

It was possible to include patients in either trial before results of bacterial culture were known. The following patients could not be included: patients with acute respiratory distress; cystic fibrosis or lung disease linked to *Pneumocystis carinii*; a disease that could rapidly become life-threatening (acute hepatic failure or septic shock), APACHE II score < 8 and > 25 (DORI-09) or > 29 (DORI-10); immunosuppressed patients and those who have received systemic antibiotic therapy for more than 24 hours of the 72 hours (DORI-09) or 48 hours (DORI-10) prior to inclusion, and patients requiring concomitant systemic antibiotic therapy.

**Treatments**

Patients were randomised, following stratification by geographical area, ventilation method and severity of disease (APACHE II) to receive the following open-label treatment:

**In study DORI-09**

- doripenem, as a 1-hour perfusion at a dose of 500 mg every 8 hours;
- piperacillin-tazobactam, as a 30-minute perfusion at a dose of 4.5 g every 6 hours.

**In study DORI-10**

- doripenem, as a 4-hour perfusion at a dose of 500 mg every 8 hours;
- imipenem, as a 30-minute perfusion at a dose of 500 mg every 6 hours or as a 1-hour perfusion at a dose of 1000 mg every 8 hours.

Patients were required to receive treatment for a period of 7-14 days (IV alone in study DORI-10 or IV ± PO in study DORI-09).

Amikacin could be added when starting IV treatment if infection involving *Pseudomonas aeruginosa* was suspected. Vancomycin can be added in case of methicillin-resistant *Staphylococcus aureus* infection (MRSA).

After 72 hours of IV treatment, patients could be switched to oral treatment (levofloxacin 750 mg/day) if there was clinical improvement (DORI-09 study).

**Primary endpoint**: clinical cure evaluated at test-of-cure (TOC) visit (6-20 days after end of IV + oral treatment), in the clinically evaluable population (CE) and in the clinically modified intention-to-treat population (cMITT). Clinical cure was defined as "resolution of signs and symptoms of infection and improvement or lack of progression of all chest x-ray abnormalities, such that no additional antibacterial therapy was required for the treatment of the current infection."

---


Results

- Study populations

<table>
<thead>
<tr>
<th></th>
<th>DORI-09 study</th>
<th>DORI-10 study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DORIBAX</td>
<td>DORIBAX</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>225</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td>223</td>
<td>267</td>
</tr>
<tr>
<td>imipenem/cilastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>264</td>
<td>267</td>
</tr>
<tr>
<td></td>
<td>262</td>
<td>263</td>
</tr>
</tbody>
</table>

| Randomised, n       | 225           | 264           |
| Intention-to-treat population (ITT), n | 223           | 262           |
| Clinically modified intention-to-treat population (cMITT), n (%) | 217 (97.3) | 249 (95.0) |
| Clinically evaluable population (CE), n (%) | 134 (60.1) | 126 (48.1) |
| Microbiologically evaluable (ME), n (%) | 84 (37.7) | 116 (44.3) |

ITT: randomised subjects who have received at least one dose of antibiotic.

cMITT: All randomized patients who received any amount of study drug therapy and met the minimal disease definition of pneumonia.

CE: all randomized patients who received an adequate course of study drug therapy, who met the protocol-specified disease definition of NP, and for whom sufficient information was available to determine the patient’s clinical outcome at the TOC visit.

ME: microbiologically evaluable (ME): A subset of the CE at TOC analysis set presenting with at least 1 adequate baseline bacterial pathogen, susceptible to both IV study drug therapies.

Demographic and disease characteristics were similar between treatment arms, but differed between the studies.

In DORI-09, median patient age was 61 years (18-97, of whom 44.6% were ≥ 65 years, 68% men). 78% of patients were not ventilated, and the 22% who were on ventilation had been on ventilation for less than 5 days. The majority of patients had no bacteraemia on inclusion (94% in the DORIBAX group vs 85.7% in the piperacillin/tazobactam group). APACHE II score was >15 in just 19% of patients and > 20 in 6.3% of patients.

Around 78% of patients in the DORIBAX group and 85% in the piperacillin/tazobactam arm received additional therapy with amikacin for proven or likely *P. aeruginosa* infection. Vancomycin was given as an additional treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) in 13% of patients in the DORIBAX arm and 18% in the piperacillin/tazobactam arm. 41% of patients were switched to oral levofloxacin therapy; these patients received a mean of 7 days of IV treatment before the switch, giving a total duration (IV + PO) of 11 days on average.

In DORI-10, median patient age was 50 years (18-86, of whom 28.6% were ≥ 65 years, 78% men). The majority of patients did not have bacteraemia on inclusion (90% in both arms). APACHE II score was <15 in half of patients (48%), > 20 in 21% of patients and > 25 in 0.8% of patients.

At least one concomitant antibiotic therapy was received by 81% of patients in the CE population (of whom 33% were considered to have failed treatment). Around 22% of patients received additional antibiotic therapy for proven or likely *P. aeruginosa* infection, and 28% for MRSA.

The most commonly identified pathogens in both studies (> 10 patients) were: *S. aureus, H. influenzae, P. aeruginosa, K. pneumoniae, E. coli, Enterobacter cloacae, A. baumanii et S. pneumoniae.*
### Clinical and microbiological success rate

<table>
<thead>
<tr>
<th></th>
<th>DORI-09 study</th>
<th>DORI-10 study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients on or not on assisted ventilation</td>
<td>Patients on assisted ventilation</td>
</tr>
<tr>
<td><strong>DORIBAX</strong></td>
<td>Piperacillin/tazobactam*</td>
<td>DORIBAX</td>
</tr>
<tr>
<td><strong>Clinical cure CE, %</strong></td>
<td>81.3 (109/134)</td>
<td>79.8 (95/119)</td>
</tr>
<tr>
<td>(n/N)</td>
<td>Difference: 1.5; 95% CI [-9.1; 12.1]</td>
<td>Difference: 3.5 [-9.1; 16.1]</td>
</tr>
<tr>
<td><strong>Clinical cure cMITT, %</strong></td>
<td>69.5 (148/213)</td>
<td>64.1 (134/209)</td>
</tr>
<tr>
<td>(n/N)</td>
<td>Difference: 5.4; 95% CI [-4.1; 14.8]</td>
<td>Difference: 1.2 [-7.9; 10.3]</td>
</tr>
<tr>
<td><strong>Microbiological response ME, % (n/N)</strong></td>
<td>84.5 (71/84)</td>
<td>80.7 (67/83)</td>
</tr>
<tr>
<td>(n/N)</td>
<td>Difference: 3.8; 95% CI [-8.9; 16.5]</td>
<td>Difference: 6.0 [-6.8; 18.8]</td>
</tr>
</tbody>
</table>

* ± amikacin (in cases of *P. aeruginosa* infection) or vancomycin (in cases of *MRSA* infection).

In both studies, DORIBAX was non-inferior to comparator treatments (piperacillin/tazobactam and imipenem/cilastatin) in terms of rates of clinical cure evaluated at test-of-cure (TOC) visit (6-20 days after end of IV + oral treatment), in the clinically evaluable population (CE) and in the clinically modified intention-to-treat population (cMITT).

Analysis of the secondary endpoints (in particular microbiological response) and sub-group analysis confirm that DORIBAX is non-inferior to comparators. Analysis of the microbiological response in the ME population in terms of the relevant pathogen involved a very limited number of patients (< 20 patients per pathogen isolated in each treatment arm), which means that no conclusions can be drawn.

In DORI-10, all-cause mortality rates were comparable in the two treatment arms in the ITT population (13% versus 12%).

It should be noted that clinical data are limited for severe forms (APACHE II > 20), and that there are no data (because of non-inclusion criteria) in patients with poor prognosis, e.g. septic shock, associated respiratory distress, or underlying serious health condition (e.g. immunosuppression, cystic fibrosis).

#### 3.1.2. Complicated abdominal infections

The clinical development program is based on two controlled studies, the aim of which was to demonstrate non-inferiority (delta threshold = 15 %) of doripenem (DORIBAX) to meropenem (study DORI-07\(^3\) and DORI-09).

**Study features**

**Populations**

Adult patients with localised or generalised peritonitis secondary to perforated appendix, perforation of the small or large intestine, cholecystitis or parenchymatous abscess (including liver and spleen). It was also possible to include patients who required planned surgery within 24 hours.

The following could not be included: simple cholecystitis; infected cholecystitis with no wall rupture; simple appendicitis; acute suppurative cholangitis; necrotising infectious pancreatitis, pancreatic abscess; abdominal infection thought to be caused by at least one bacterial strain that is resistant to one of the study treatments, APACHE score >30, patients who had received systemic antibiotics for more than 24 hours in the 2 days prior to inclusion, patients with a life-threatening or rapidly progressing disease (acute liver failure, septic shock, respiratory failure), signs of immunosuppression.

---

Treatments
Patients were randomised, following stratification by geographic region, infection site (complicated localised appendicitis versus other abdominal infection sites) and by severity of infection (APACHE II score ≤ 10 or > 10), to receive as double-blind treatment:
- doripenem, administered as a one-hour perfusion at a dose of 500 mg/8 hours
- meropenem, administered as a 3-5 minute bolus at a dose of 1 g/8 hours

Given these different perfusion times, each treatment was given with a placebo in order to maintain the double blind.

After 72 hours of treatment, it was possible to switch patients to oral treatment (amoxicillin/clavulanic acid) if response to treatment was favourable. Patients were able to receive concomitant treatment with vancomycin (open-label) if one of the bacteria isolated was an enterococcus or methicillin-resistant S. aureus.

Patients had to receive treatment for 5-14 days. Persistent symptoms of infection after 14 days of antibiotic therapy, requiring antibiotic treatment, was considered to be treatment failure.

Primary endpoint: rate of clinical cure at the test-of-cure visit (21-60 days after treatment) in the microbiologically evaluable population (ME); rate of clinical cure occurring up to 60 days after the last dose in the microbiologically modified ITT population (mMITT).

Results
Of the 476 (DORI-07) and 486 (DORI-09) subjects randomised, 319 and 315 were included in the ME population.

Demographic and baseline characteristics were generally similar between treatment groups and between the studies.

Median patient age was 45 years (18-94, of whom 16.7% were ≥ 65 years, 63.4% men). The main source of infection was the appendix (62% of patients treated with DORIBAX) and of these patients, 51% had generalised peritonitis on inclusion. Other sources of infection included perforation of the colon (20%), complicated cholecystitis (5%) and infections in other sites (14%). Only 9.5% had post-operative infections, 27% had single or multiple abdominal abscesses and 4% had concomitant bacteraemia on inclusion. Around 90% of patients had an APACHE II score of < 10, which means a low level of severity.

Of the 634 subjects included in the ME population, 75% were switched to oral treatment from IV treatment. Mean duration of IV treatment was 5.7 days and mean duration of IV + PO treatment was 11 days.

- Clinical and microbiological success rate

<table>
<thead>
<tr>
<th></th>
<th>DORI-07</th>
<th></th>
<th>DORI-08</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DORIBAX</td>
<td>Meropenem</td>
<td>DORIBAX</td>
<td>Meropenem</td>
</tr>
<tr>
<td>Clinical cure ME, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n/N)</td>
<td>85.9 (140/163)</td>
<td>85.3 (133/156)</td>
<td>83.3 (135/162)</td>
<td>83.0 (127/153)</td>
</tr>
<tr>
<td>Difference:</td>
<td>0.6; 95% CI [-7.7; 9.0]</td>
<td></td>
<td>0.3 [-8.6; 9.2]</td>
<td></td>
</tr>
<tr>
<td>Clinical cure mMITT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>77.9 (152/195)</td>
<td>78.9 (150/190)</td>
<td>74.5 (149/200)</td>
<td>75.7 (140/185)</td>
</tr>
<tr>
<td>Difference:</td>
<td>-1.1; 95% CI [-9.7; 7.7]</td>
<td></td>
<td>-1.2 [-10.3; 8.0]</td>
<td></td>
</tr>
<tr>
<td>Clinical cure CE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>86.7 (163/188)</td>
<td>86.6 (161/186)</td>
<td>83.9 (161/192)</td>
<td>85.9 (165/192)</td>
</tr>
<tr>
<td>Difference:</td>
<td>0.1; 95% CI [-7.3; 7.6]</td>
<td></td>
<td>-2.1 [-9.8; 5.6]</td>
<td></td>
</tr>
<tr>
<td>Microbiological response ME</td>
<td>85.3 (139/163)</td>
<td>84.6 (132/156)</td>
<td>83.3 (135/162)</td>
<td>84.3 (129/153)</td>
</tr>
<tr>
<td>Difference:</td>
<td>0.7; 95% CI [-7.8; 9.1]</td>
<td></td>
<td>-1.0 [-9.7; 7.8]</td>
<td></td>
</tr>
</tbody>
</table>

4 mMITT: Patients in the cMITT arm in whom at least one sensitive bacterial strain was identified.
In both studies, DORIBAX was non-inferior (delta threshold = 15%) to meropenem in terms of rate of clinical cure at the test-of-cure visit (21-60 days after treatment) in the microbiologically evaluable population (ME) and in terms of rate of clinical cure occurring up to 60 days after the last dose in the mMITT (primary endpoints).

Analysis of the secondary endpoints (particularly microbiological response) and sub-group analysis (particularly microbiological response in the ME population by pathogen) confirm that DORIBAX is non-inferior to meropenem.

All-cause mortality rates were comparable in the two treatment arms in both studies (2% in the doripenem arm and 3% in the meropenem arm).

### 3.1.3. Complicated urinary tract infections (cUTI)

The clinical development program is based on two studies (DORI-05 and DORI-06), the aim of which was to demonstrate the efficacy of DORIBAX in the treatment of complicated lower urinary tract infections and pyelonephritis.

- DORI-05 was a controlled non-inferiority study (delta threshold = 10%), comparing the efficacy of DORIBAX with levofloxacin,
- DORI-06 was a non-comparative study. Patients were compared with the levofloxacin arm of DORI-05.

#### Study features

**Populations**

Adult patients with clinical signs of urinary tract infection (pyelonephritis or complicated lower urinary tract infection) and positive culture of a urinary pathogen (>10^5 CFU/mL) within the 48 hours prior to the first dose of study treatment.

The following could not be included: patients with permanent or complete obstruction of the urinary tract; those with a catheter in the bladder; patients with suspected or confirmed prostatitis, and those with signs of immunosuppression.

**Treatments**

In DORI-05, patients were randomised, after stratification by type of urinary tract infection (complicated lower urinary tract or pyelonephritis) and the nature of their infection symptoms for those with complicated lower urinary tract infections, to receive as double-blind treatment:

- doripenem, as a 1-hour perfusion at a dose of 500 mg every 8 hours;
- levofloxacin, as a 1-hour perfusion at a dose of 250 mg every 24 hours.

Given these different perfusion times, each treatment was given with a placebo in order to maintain the double blind.

After 9 doses of IV treatment, it was possible to switch patients to oral therapy (levofloxacin 250 mg/day po) if there had been no fever for at least the previous 24 hours, if clinical signs/symptoms had improved or if laboratory parameters were acceptable.

Patients had to receive treatment for 10 days (IV + oral) or up to 14 days for patients with concomitant bacteraemia.

In DORI-06, patients received DORIBAX under the same treatment regimen.

**Primary endpoint**: bacteriological cure rate (=eradication of all urinary pathogens identified at the time of inclusion) evaluated at the test-of-cure visit (5-11 days after treatment in DORI-05 and 6-9 days in DORI-06) in the microbiologically evaluable population and in the mMITT.

#### Results

Seven hundred and fifty three (753) subjects were randomised in DORI-05 and 426 subjects were included in DORI-06.

The main demographic and medical characteristics of included patients were similar in all treatment arms. Patients were mostly women, with a mean age of 55 years (of whom around 15% were over 75). The most frequently isolated pathogen in both studies was E. coli (11% were resistant to levofloxacin, and 0% to doripenem). The percentage of patients with a positive blood culture was low (9%). In terms of renal function on inclusion, 18% of patients in DORI-06 and 13% in DORI-05 had moderate to severe renal insufficiency (creatinine clearance < 50 mL/min).
Of the 795 subjects in the ME population, 83% were switched to oral treatment (levofloxacin 250 mg/day) after a mean IV treatment duration of 5 days (total duration of IV + oral treatment was 10 days).

- **Medical characteristics of patients on inclusion**

<table>
<thead>
<tr>
<th>Diagnosis at inclusion, n (%)</th>
<th>DORIBAX N = 280</th>
<th>Levofloxacin N = 265</th>
<th>DORIBAX N = 250</th>
<th>DORIBAX N = 530</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>280</td>
<td>265</td>
<td>250</td>
<td>530</td>
</tr>
<tr>
<td>cLUTI*</td>
<td>145 (51.8)</td>
<td>131 (49.4)</td>
<td>132 (52.8)</td>
<td>277 (52.3)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>135 (48.2)</td>
<td>134 (50.6)</td>
<td>118 (47.2)</td>
<td>253 (47.7)</td>
</tr>
<tr>
<td>Complicated pyelonephritis</td>
<td>21 (15.6)</td>
<td>27 (20.1)</td>
<td>19 (16.1)</td>
<td>40 (15.8)</td>
</tr>
<tr>
<td>Uncomplicated pyelonephritis</td>
<td>114 (84.4)</td>
<td>107 (79.9)</td>
<td>99 (83.9)</td>
<td>213 (84.2)</td>
</tr>
<tr>
<td>Bacteraemia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>280</td>
<td>265</td>
<td>250</td>
<td>530</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (7.1)</td>
<td>23 (8.7)</td>
<td>27 (10.8)</td>
<td>47 (8.9)</td>
</tr>
<tr>
<td>No</td>
<td>260 (92.9)</td>
<td>242 (91.3)</td>
<td>223 (89.2)</td>
<td>483 (91.1)</td>
</tr>
</tbody>
</table>

*complicated lower urinary tract infection

- **Microbiological and clinical cure rates**

<table>
<thead>
<tr>
<th></th>
<th>DORI-05 study</th>
<th>DORI-06 study</th>
<th>DORIBAX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DORIBAX 500 mg/8h</td>
<td>Levofloxacin* 250 mg/day</td>
<td>DORIBAX</td>
</tr>
<tr>
<td>Bacteriological cure</td>
<td>82.1 (230/280)</td>
<td>83.4 (221/265)</td>
<td>83.6 (209/250)</td>
</tr>
<tr>
<td>ME, % (n/N)</td>
<td>Difference: -1.3; 95% CI [-8.0; 5.5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriological cure</td>
<td>79.2 (259/327)</td>
<td>78.2 (251/321)</td>
<td>82.5 (278/337)</td>
</tr>
<tr>
<td>mMITT</td>
<td>Difference: 1.0; 95% CI [-5.6; 7.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure CE</td>
<td>95.1 (272/286)</td>
<td>90.2 (240/266)</td>
<td>93.0 (239/257)</td>
</tr>
<tr>
<td></td>
<td>Difference: 4.9; 95% CI = [0.2; 9.6].</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In DORI-05, DORIBAX was non-inferior (delta threshold = 10%) to levofloxacin (250 mg/day) in terms of bacteriological cure rates (= eradication of all urinary pathogens identified on inclusion) at the test-of-cure visit (5-11 days after treatment) in the microbiologically evaluable population and in the mMITT population.

Analysis of the secondary endpoints (in particular clinical cure) and sub-group analysis (in particular microbiological response in terms of urinary pathogen/E. coli and clinical diagnosis at time of inclusion) confirm the results observed for the primary endpoints.

Results of the DORI-06 study, confirm the microbiological and clinical response observed in DORI-05.

However, in France, the dosage of levofloxacin used in the treatment of pyelonephritis is 500 mg/day (and not 250 mg/day, as stated in the dossier). The dose of 500 mg/day is considered to be optimal (see levofloxacin SPC). For this reason, the results of this “non-inferiority” study must be interpreted with care.

### 3.2. Safety

**Clinical experience** (see SPC)

Evaluation of the safety profile of DORIBAX in use is based on clinical data from phase 2 and 3 studies (3142 adult patients) in which 1817 patients were treated with DORIBAX at a dose of 500 mg every 8 hours.

The incidence of adverse effects observed for DORIBAX was 32%. The most frequent adverse effects varied by indication, and were similar to comparator products: headache (10%), diarrhea (9%) and nausea (8%). DORIBAX was discontinued because of an adverse effect in 0.1% of
patients. Adverse effects leading to discontinuation of DORIBAX were as follows: nausea (0.1%), diarrhea (0.1%), itching (0.1%), fungal infection of the vulva (0.1%), increased liver enzymes (0.2%) and skin eruption (0.2%). In general, the data from the various studies did not demonstrate any unexpected adverse effects in comparison with other carbapenem antibiotics.

3.3. Conclusion

- Nosocomial pneumonia
  Studies of nosocomial pneumonia showed that doripenem (DORIBAX, 500 mg/8h as a 1 or 4-hour perfusion) was non-inferior (delta threshold = 20%) to piperacillin-tazobactam (DORI-09) in patients with early-onset nosocomial pneumonia (not ventilated or ventilated for < 5 days) and to imipenem-cilastatin (DORI-10) in patients with nosocomial pneumonia on assisted ventilation, around 60% of whom had been on ventilation for ≥ 5 days (late-onset NP). The characteristics of patients included in both studies reflected a population with non-severe disease (DORI-09) or moderately severe disease (DORI-10), with a very limited number of patients with a high APACHE II score (21% > 20 and 0.8% > 25).
  When IV treatment was initiated, patients received additional antibiotic therapy with amikacin if *Pseudomonas aeruginosa* infection was suspected, or with vancomycin if methicillin-resistant *S. aureus* was suspected.

  Rates of clinical cure (primary endpoint) evaluated 6-20 days after discontinuation of treatment (IV + oral) were:
  - DORI-09: in the clinically evaluable population (CE) 81.3 % (doripenem) versus 79.8% (piperacillin-tazobactam), difference = 1.5; 95% CI [-9.1; 16.1] and in the clinically modified intention-to-treat population (cMITT) it was 69.5 % versus 64.1 % (difference: 5.4% [-4.1; 14.8]).
  - DORI-10 study: 68.3 % versus 64.8 (difference: 3.5 [-9.1; 16.1]) in the CE population; and 59.0 % versus 57.8% (difference: 1.2 [7.9; 10.3]) in the cMITT population.

  In DORI-10, the all-cause mortality rate was low (13% versus 12%) in comparison with the mortality rates described for patients who developed nosocomial pneumonia (mortality between 30% and 60%)\(^5\).
  It should be noted that there is a limited number of cases of infection caused by multiresistant bacteria, and that there has been no evaluation (because of non-inclusion criteria) of patients with poor prognosis, e.g. septic shock, associated respiratory distress, or underlying serious health condition (e.g. immunosuppression, cystic fibrosis).

- Complicated abdominal infections
  Studies that have been carried out (DORI-07, DORI-08) showed that doripenem is non-inferior (delta threshold = 15%) to meropenem (DORIBAX 500 mg/8h given as a 1h or 4h perfusion, meropenem given 1 g/8 h, as a 3-5 minute bolus). The majority of patients (75%) were switched to oral treatment (with amoxicillin + clavulanic acid) after a mean IV treatment duration of 5.7 days (duration of IV + oral treatment was 11 days). Around 90% of patients included in this study had an APACHE II score of < 10, which means a low level of severity.

  Rates of clinical cure (primary endpoint) evaluated 21-60 days after discontinuation of treatment (IV + oral) were:
  - DORI-07: in the microbiologically evaluable population (ME) 85.9% (doripenem) versus 79.8% (meropenem), difference = 0.6; 95% CI [-7.7; 9.0] and in the microbiologically modified intention-to-treat population (mMITT) it was 77.9% versus 78.9% (difference: -1.1% [-9.7; 7.7]).
  - DORI-08: in the ME population 83.3% versus 83.0% (difference: 0.3 [-8.6; 9.2]) and in the mMITT population 74.5 % versus 75.7% (difference: -1.2 [-10.3; 8.0])

  The mortality rate was low (2 vs 3%) in comparison with rates usually seen in "really" serious infections (of the order of 5-15% for community-acquired peritonitis and in excess of 40% for post-operative peritonitis).

Complicated urinary tract infections

In DORI-05, doripenem (DORIBAX) was non-inferior (delta threshold = 10%) to levofloxacin (250 mg/day) in terms of bacteriological cure rates (= eradication of all urinary pathogens identified on inclusion) at the test-of-cure visit (5-11 days after treatment) in the microbiologically evaluable population (82.1% versus 83%, difference -1.3 [-8.0; 5.5]) and in the mMITT population (79.2% versus 78.2%, difference 1.0 [-5.6; 7.6]). Results of the DORI-06 study, which was non-comparative, confirm the microbiological and clinical response observed in DORI-05.

However, it should be noted that there was insufficient documentation of the efficacy of doripenem in the treatment of acute complicated pyelonephritis (with e.g. septic shock, abscess, renal failure) or associated with a risk factor for complications (e.g. diabetes, immunosuppression, age > 65 years, malformation of the renal excretory system). The majority (84%) of cases of pyelonephritis treated in the various trials were simple pyelonephritis. Moreover, the dose of levofloxacin used in this trial (250 mg/day) does not correspond to the levofloxacin dosage (500 mg/day) that is recommended in France for the treatment of acute pyelonephritis (see levofloxacin SPC). The dose of 500 mg/day is considered to be optimal. For this reason, the results of this "non-inferiority" study must be interpreted with care.

Safety: the data from the various studies did not demonstrate any unexpected adverse effects in comparison with other carbapenem antibiotics. The most commonly observed adverse effects were digestive problems (diarrhea, nausea) and headaches.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The conditions treated by this medicinal product can be immediately life-threatening or may cause fatal complications.

This product is intended to provide curative treatment.

For non-severe or moderately severe forms of disease, the efficacy/adverse effects ratio is high. For severe forms, the efficacy/adverse effects ratio has yet to be determined.

For each of the various indications, there are therapeutic alternatives, including for treatment of multiresistant organisms.

Public Health Benefit

The public health burden represented by patients with nosocomial pneumonia or complicated abdominal infections or complicated urinary tract infections can be considered to be moderate. The burden represented by patients with severe forms and/or forms caused by multiresistant bacteria is low, because of the restricted numbers involved.

Making new agents available to combat the spread of pathogenic bacteria that have acquired resistance to antibiotics is a public health need.

Given the available data, DORIBAX is not expected to have an additional impact on morbidity and mortality in comparison to therapeutic agents used in current clinical practice. In addition, it is not certain that the experimental data can be transposed to clinical practice, as the patients included in the trials were not representative of those who would require treatment with DORIBAX in practice (those with severe disease).

The proprietary product DORIBAX is not therefore expected to provide an additional response to an identified public health need.

Consequently, DORIBAX is not expected to benefit public health in these indications.
The actual benefit provided by this product in the treatment of late-onset nosocomial pneumonia and complicated abdominal and urinary tract infections caused by multiresistant bacteria that are sensitive to doripenem is substantial.

4.2. Improvement in actual benefit

Given the currently available data, DORIBAX has not been shown to provide an improvement in actual benefit in comparison with therapeutic agents currently used to treat nosocomial pneumonia or complicated abdominal and urinary tract infections (IAB V).

DORIBAX is an useful additional therapeutic tool in the carbapenem class, which provides a broader selection of therapeutic possibilities in the treatment of multiresistant Gram negative bacteria such as Pseudomonas.

4.3. Therapeutic use

4.3.1. Therapeutic strategy for nosocomial pneumonia (NP)

In cases of documented NP, antibiotic therapy is adapted to the isolated infectious agents. Dual therapy may be justified in order to broaden the spectrum of drug activity and reduce the risk of emergence of resistant strains. Dual therapy is essential for infection with *Pseudomonas* sp, enterobacteria such as *Enterobacter* sp, *Klebsiella* sp, *Serratia* sp, or use of fosfomycin, fusidic acid, fluoroquinolones, or rifampicin.

In cases of non-documented NP, the choice of empirical antibiotic therapy depends primarily on the time to onset (early or late-onset pneumonia) and any prior antibiotic therapy. Choice of therapy must also take into account the background (chronic respiratory failure, cystic fibrosis, immunosuppression, neutropenia), and the microbiological environment in the ward.

Recognition of some etiological risk factors will help to choose a suitable empirical antibiotic regimen: coma (*S. aureus*), immunosuppression, use of steroids (*L. pneumophila*), chronic obstructive pulmonary disease (COPD), assisted ventilation for more than 8 days, previous broad-spectrum antibiotic treatment (*P. aeruginosa*), neurosurgery, head trauma, inhalation, prior broad-spectrum antibiotic treatment (*A. baumannii*), altered consciousness (anaerobes).

The major aspects of management are summarised in the table below.

In all cases, initial antibiotic therapy must be re-evaluated as soon as bacteriological results are obtained, and if possible triple therapy should be reduced to dual therapy, or broad-spectrum therapy reduced to a narrower spectrum.

The usual recommended duration of treatment is 7 days. If there is multilobar necrotic disease involving *P. aeruginosa* or *Acinetobacter* sp, the duration of treatment is increased to 2 weeks. Initial combination treatment with aminoside can be discontinued after 4-5 days of treatment, and the antibiotic alone can be used for the rest of the treatment period.

---

6 Nosocomial pneumonia (NP) can be classified (E. Pill 2006) according to time to onset from admission date, and whether or not the patient has received antibiotic therapy within the previous 15 days. If onset is before the 5th day (early-onset NP), the infectious agents are endogenous flora (*S. pneumoniae, H. influenzae, methicillin-sensitive Staphylococci, Escherichia coli*). Beyond this time (late-onset NP), exogenous flora found in the hospital environment also cause disease (*Pseudomonas sp, Acinetobacter sp, methicillin-resistant Staphylococci, Klebsiella sp, Enterobacter sp, Serratia sp*). If the patient has received antibiotic treatment within the previous 15 days, the possibility of resistant organisms must be considered, regardless of whether the 5-day threshold has been reached. Late-onset nosocomial pneumonia can lead to excess mortality, linked to higher quantities of multiresistant micro-organisms and a higher risk that antibiotic therapy will not be sufficient to eradicate the pathogen.

### Empirical Antibiotic Therapy for Nosocomial Pneumonia

<table>
<thead>
<tr>
<th>Early onset NP</th>
<th>No prior antibiotic therapy</th>
<th>With prior antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td>C3G or amoxicillin + clavulanic acid</td>
<td>Dual therapy</td>
</tr>
<tr>
<td><strong>Suspected GNB</strong></td>
<td>[anti-Pseudomonas beta-lactam(^1)] + [aminoside or ciprofloxacin]</td>
<td><strong>Suspected GNB</strong></td>
</tr>
<tr>
<td>Late onset NP</td>
<td><strong>Monotherapy</strong></td>
<td><strong>Dual therapy</strong></td>
</tr>
<tr>
<td>Non-severe</td>
<td>- Suspected GNB</td>
<td><strong>Triple therapy</strong></td>
</tr>
<tr>
<td>Severe</td>
<td>[anti-Pseudomonas beta-lactam(^1)] + [aminoside or ciprofloxacin]</td>
<td>+ glycopeptide/linezolid</td>
</tr>
</tbody>
</table>

\(^1\) anti-Pseudomonas beta-lactam: ceftazidine, cefepime, piperacillin+tazobactam

\(^2\) In addition to the substances mentioned above, imipenem can be added

\(^3\) A combination of quinupristine + dalfopristine can be given as an alternative

---

### Place of doripenem (DORIBAX) in therapeutic strategy

DORIBAX will have a similar prescription profile to imipenem, because of its in vitro activity spectrum and the clinical data that have been presented, which suggest that it will have similar efficacy and safety to imipenem in the treatment of late-onset nosocomial pneumonia. However, clinical data are limited for severe forms (APACHE II > 20) and forms caused by multiresistant bacteria, and there are no data (because of non-inclusion criteria) in patients with poor prognosis, e.g. septic shock, associated respiratory distress, or underlying serious health condition (e.g. immunosuppression, cystic fibrosis).

### 4.3.2. Complicated abdominal infection and complicated urinary tract infections

Standard treatment consists of antibiotics that are suitable for treatment of identified or likely bacteria. There are many possible choices\(^8,9\), depending on the bacteria and their level of resistance. It is difficult to state the precise role of DORIBAX currently, as there is insufficient data about its clinical efficacy in infections that are severe and/or caused by multiresistant bacteria.

For the indications given in the marketing authorisation, DORIBAX use would be mainly reserved for patients requiring intravenous treatment for infection with multiresistant bacteria that are sensitive to doripenem, and particularly where there is no therapeutic alternative.

### 4.4. Target Population

The indications for DORIBAX are nosocomial pneumonia (including ventilation pneumonia), as well as complicated abdominal and urinary tract infections managed during hospital admission.

It is currently difficult to define the target population for DORIBAX precisely, as there is insufficient data about its clinical efficacy.

According to the national survey concerning the prevalence of nosocomial infections (InVS, June 2006)\(^10\), nosocomial infections affected 5% of patients admitted to French healthcare facilities\(^11\). The most common nosocomial infections (59% in all) were urinary tract infections (30%), pneumonia (15%) and operation site infection (14%).

In practice, use of DORIBAX should be reserved for treatment of late-onset severe nosocomial pneumonia or nosocomial pneumonia caused by multiresistant organisms (beta-lactamase secreting Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter sp.*) as an alternative to the other carbapenems. DORIBAX can also, very occasionally, be an alternative to first-line

\(^8\) Management of community-acquired peritonitis - Consensus conference - SFAR 16 June 2000


\(^11\) This survey does not include day cases or home hospital care, or care in post-admission care facilities.
antibiotics in the treatment of severe abdominal and urinary infections caused by multiresistant organisms that are sensitive to doripenem and for which intravenous treatment is required.

If the prevalence of nosocomial pneumonia is extrapolated to all recorded hospital admissions in 2006 in the PMSI (public and private databases), with the exception of admissions lasting less than 24 hours, i.e. 8,775,009 admissions, the number of cases of nosocomial pneumonia in France can be estimated as around 65,000 patients. The risk factors mainly relate to assisted ventilation. The incidence of ventilation-acquired nosocomial pneumonia is difficult to determine. It varies depending on the populations studied and the diagnostic methods used, with a mean of 30%\textsuperscript{12} and around 50% of patients having been ventilated for 5 days or more\textsuperscript{13}, giving a total of around 10,000 patients with late-onset nosocomial pneumonia.

We have no epidemiological data that would enable us to determine the incidence of severe forms or forms caused by multiresistant bacteria.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication of Marketing authorisation.
