



11th July 2012

**Direct Healthcare Professional Communication -
New recommendations on dosing, duration and precautions for treatment of
patients with Nosocomial Pneumonia with DORIBAX[®] (doripenem)**

Dear Healthcare Professional:

Summary

- **Recent study data indicate that the currently approved dose of 500 mg every 8 hours as a 1 or 4-hour infusion is not sufficient in all patients with nosocomial pneumonia (NP).**
- **A doripenem dose of 1 g every 8 hours infused as a 4-hour infusion may be considered when treating NP (including ventilator-associated pneumonia - VAP) in patients with creatinine clearance \geq 150 ml/min and/or infections with non-fermenting gram-negative pathogens**
- **A treatment duration of 10-14 days is usually required for patients with NP, including VAP.**

This communication has been endorsed by the Committee for Medicinal Products for Human Use (CHMP).

Further information

The DORIBAX[®] dosing recommendations of 500 mg every 8 hours as a 1- or 4-hour infusion for the treatment of patients with NP (including VAP) are based on two pivotal Phase 3 clinical studies, the data from which were included in the initial marketing authorisation application.

More recently, a study (DORINOS3008) of 233 patients with late-onset VAP failed to demonstrate the non-inferiority of an investigational fixed 7-day course of doripenem (1 g every 8 hours as a 4 hour infusion) compared to a fixed 10-day course of imipenem/cilastatin (1 g every 8 hours as a 1 hour infusion). In addition, the patients were allowed to receive specified adjunctive therapies. The study was stopped early based on the recommendation of an independent data monitoring committee. The clinical cure rate at the end of treatment visit on day 10 was numerically lower for subjects in the doripenem arm of the primary microbiological intent-to-treat (MITT) (45.6% versus 56.8%; 95% CI: -26.3%;

3.8%) and co-primary microbiologically evaluable (ME) (49.1% [28/57] versus 66.1% [39/59]; 95% CI -34.7%; 0.8%) analysis sets. The overall 28-day all cause mortality rate was numerically higher for doripenem treated subjects in the MITT analysis set (21.5% versus 14.8%; 95% CI: -5.0%; 18.5%). The difference in clinical cure rate between doripenem versus imipenem/cilastatin was greater in patients with APACHE II score >15 (16/45 [36%] versus 23/46 [50%]) and in patients infected with *Pseudomonas aeruginosa* 7/17 [41%] versus 6/10 [60%]).

Detailed analyses of data from all doripenem studies in patients with VAP and extensive clinical experience of carbapenem treatment in this group of patients, indicates that the short fixed duration of therapy with DORIBAX[®] was a major contributor to the inferior outcome in the doripenem group in DORINOS3008.

Based on the results from DORINOS3008, additional Phase 1 and 2 studies with 1 g dosing, and the 2 pivotal Phase 3 studies at 500 mg, the prescribing information for DORIBAX[®] has been updated to reflect that:

- the usual treatment duration for patients with NP (including VAP) is 10 to 14 days and is often in the upper range for patients infected with non-fermenting gram-negative pathogens (e.g. *Pseudomonas spp.*, *Acinetobacter spp.*).
- Based on PK/PD modeling and safety data from approximately 500 subjects, 1 g doripenem administered every 8 hours as a 4-hour infusion may be considered when treating patients with NP (including VAP), in the following instances:
 - augmented renal clearance (particularly those with creatinine clearance (CrCl) ≥150 ml/min)
 - infections by non-fermenting gram-negative pathogens
- Caution is advised when selecting doripenem to treat an individual patient and should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem resistant bacteria.
- Caution is also advised on the choice of the antimicrobial agent and dose when treating patients with late-onset VAP (>5 days hospitalisation) and in other NP cases where pathogens with decreased susceptibility are suspected or confirmed, such as *Pseudomonas spp.* and *Acinetobacter spp.*
- Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications.

The CHMP has invited the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to review the resistance breakpoint for DORIBAX[®].

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of DORIBAX[®] to the MHRA through the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-7316789
- or by electronic download through the Yellow Card section of the MHRA website www.mhra.gov.uk/yellowcard

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Suspected adverse reactions should also be reported to Janssen-Cilag Ltd. on tel: 0800-3893640, fax: 0800-3893644 or by e-mail at dsafety@its.jnj.com.

Communication information

If you have further questions, please do not hesitate to contact the Janssen Medical Information team on 0800-7318450 or medinfo@janssen-cilag.co.uk

Yours faithfully,



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