NOTICE TO HOSPITALS
Health Canada Endorsed Important Safety Information on
DORIBAX®* doripenem for Injection

January 26, 2012

To: Hospital Chief of Medical Staff

Please distribute to the relevant Departments of Surgery, Medicine, Intensive Care, Infectious Disease, Pulmonary and Respiratory Medicine, Anesthesiology, Emergency, Nursing, Pharmacy, Laboratory Services, and other involved professional staff and **post this NOTICE** in your institution.

Subject: DORIBAX® doripenem for Injection - Decreased Clinical Cure Rates and Increased Mortality in an Investigational Ventilator-Associated Pneumonia (VAP) Study

Janssen Inc., in consultation with Health Canada, would like to inform you of new safety information regarding the use of DORIBAX® in the treatment of ventilator-associated pneumonia (VAP). A prospective, randomized, double-blind, double-dummy, multicentre Phase 3 study of an investigational use of DORIBAX® in ventilator-associated pneumonia (VAP) was prematurely terminated when interim analyses of data from 274 of the planned 524 subjects showed a **higher mortality rate and a lower clinical cure rate among subjects treated with a fixed 7-day course of DORIBAX® 1 g q8h compared to those treated with a fixed 10-day course of imipenem-cilastatin.**

DORIBAX® is approved in Canada for the treatment of adults with Nosocomial Pneumonia, including VAP, complicated Intra-Abdominal Infections (cIAI) and complicated Urinary Tract Infections (cUTI), including Pyelonephritis. The approved dosage of DORIBAX® for patients with nosocomial pneumonia including VAP is 500 mg administered as a 1 or 4 hour intravenous infusion every 8 hours for 7 to 14 days.

- **The use of DORIBAX® 1 g q8h in a fixed 7-day course has been associated with a higher mortality rate and a lower clinical cure rate compared to a fixed 10-day course of imipenem-cilastatin.**
- **Treatment duration should be guided by the severity of illness, infecting pathogen and the patient's clinical response.**
- **The Canadian Product Monograph will be updated to reflect this new information.**

The Canadian Product Monograph contains information on the recommended dose and duration of treatment in the *Dosage and Administration* section. However, based on the

new information from this investigational VAP study, Janssen Inc. will be working with Health Canada to update the Product Monograph regarding the treatment of VAP.

The investigational VAP study was designed to assess the efficacy and safety of a **fixed 7-day course of doripenem** (1g, 4-hour infusion, q8h) compared with a fixed 10-day course of imipenem-cilastatin (1g, 1-hour infusion, q8h) as treatment for adult subjects hospitalized for at least 5 days and diagnosed with VAP. The primary objective of the study was to demonstrate the non-inferiority of doripenem to imipenem-cilastatin in the Microbiological Intent-to-Treat (MITT) population and the Microbiologically Evaluable (ME) population.

Table 1 below shows the interim results for both clinical cure rates and 28-day all-cause mortality rates for the MITT and ME analysis populations.

Table 1. Summary of Clinical Cure Rates and All-Cause 28-Day Mortality Rates

Analysis Population	Doripenem Group Fixed 7-day course %	Imipenem Group Fixed 10-day course %	Difference %	2-sided 95% CI %
Clinical Cure Rates				
MITT	45.6	56.8	-11.2	-26.3 to 3.8
ME	49.1	66.1	-17.0	-34.7 to 0.8
Creatinine Clearance* (MITT)				
≥ 150 mL/min	44.4	71.4	-27.0	-55.4 to 1.4
< 150 mL/min	45.9	50.0	-4.1	-21.9 to 13.7
All Cause 28-day Mortality MITT	21.5	14.8	6.7	-5.0 to 18.5

*** calculated using the Cockcroft and Gault formulas relating serum creatinine with age (in years) and body weight (in kg)**

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-market adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any cases of serious or unexpected adverse reactions in patients receiving DORIBAX® should be reported to Janssen Inc. or Health Canada.

Drug Safety Department
Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
Or call toll free at 1-866-825-7122
Or email to dsscan@joica.jnj.com
Or fax to 1-866-767-5865

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Reporting Form and:
- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section. The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties*.

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate
Email: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (Industry).

Should you have any questions or require additional information, please contact Janssen Inc. Medical Information Department at 1-800-567-3331 or 1-800-387-8781 from 9:00 am to 5:00 pm Monday to Friday Eastern Standard Time (EST) or by Fax at 416-449-2658.

Sincerely,

original signed by

Cathy Lau, PhD.
Vice President
Regulatory and Quality
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