

## Imipenem-Cilastatin for Treating Ventilator Associated Pneumonia in Egyptian Patients

### Health Technology Appraisal

Issued: September 2016

• بيانات المستحضر محل الدراسة:

Intervention	Imipenem- cilastatin
Trade name	Tienam
Company name	MERCK SHARP & DOHME- USA
Comparator	Doripenem

### • الهدف:

تقييم الفعالية لقاء التكلفة لمستحضر Imipenem- cilastatin في علاج مرضي الالتهاب الرئوي المرتبط بأجهزة التنفس الصناعي. وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية.

- علما ان الدراسة التي قامت بإجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من مناقصات هيئة التأمين الصحي، بالإضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والتبعات المحتملة عن علاج حالات الالتهاب الرئوي بأنواعها والنتيجة عن استخدام كل بروتوكول على حدة، وطبقا لتسعيرة نفقة الدولة. كما تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض "QUALITY OF LIFE" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالمياً .

بعد البحث في الأدلة العلمية وبناء على دراسة الجدوي الاقتصادية التي أجريت من قبل الوحدة وبالعرض على وحدة إقتصاديات الدواء تبين ان مستحضر Imipenem- cilastatin هو الاقل فاعلية والأكثر تكلفة مقارنة بمستحضر Doripenem في علاج مرضي الالتهاب الرئوي المرتبط بأجهزة التنفس الصناعي حيث ان مستحضر Imipenem-cilastatin هو الاعلى في التكلفة بفارق 449جنيه مصري واقل في الفاعليه بفارق 0.01 مقارنة بمستحضر Doripenem .

## **Cost-Effectiveness of Imipenem-cilastatin versus Doripenem in Ventilator Associated Pneumonia in Egyptian Patients from the Insurer perspective: A decision tree Model**

### • **Introduction**

Ventilator-associated pneumonia (VAP), the most common nosocomial infection acquired in the intensive care unit (ICU), accounting for 45% of all infections in European ICUs, is associated with high mortality rates, increased hospital stays, significantly longer duration of mechanical ventilation, and increased healthcare costs (1).

Between 10 and 20% of US patients receiving more than 48 hours of mechanical ventilation will develop VAP, and mortality is twice as high among critically ill patients who develop VAP compared with those who do not (1); the VAP-attributable mortality among VAP patients who die in hospital in the US is estimated to be between 30 and 55% (6). VAP is estimated to increase hospital stays by 4–13 days leading to additional costs (2).

Carbapenems are bactericidal against Gram-negative pathogens that commonly cause VAP, including *P. aeruginosa*, and are, therefore, recommended for initial empiric therapy for VAP. Imipenem-cilastatin (IMI) is one of the most frequently used and recommended first-line therapies for hospital acquired pneumonia (HAP) and VAP in patients at high risk for resistant pathogen (3).

Recently, *Pseudomonas aeruginosa* (PA) resistance to IMI has become an increasing challenge in VAP treatment. Newer-generation carbapenems, such as doripenem (DOR), exhibit enhanced in vitro potency against PA and a more favorable sensitivity pattern among PA isolates (4).

In evaluating comparable treatments, it has become increasingly important to understand not only efficacy but the costs of interventions aimed at reducing mortality and morbidity of critically ill patients. The study was conducted to evaluate the cost-effectiveness of Imipenem-cilastatin to help guidance in the decision-making of the reimbursement process of these drugs.

### • **Objective**

The objective of this study was to evaluate the cost-effectiveness of Imipenem-cilastatin versus Doripenem in Ventilator Associated Pneumonia from the insurer perspective over a time horizon of 15 days.

### • **Economic evaluation Key Features:**

<b>Key Features:</b>	
<b>Title and year of the document</b>	October 2016
<b>Affiliation of authors</b>	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
<b>Purpose of the document</b>	Evaluation the cost-effectiveness of using Imipenem-cilastatin versus Doripenem in Ventilator Associated Pneumonia in Egyptian patients
<b>Standard reporting format included</b>	yes
<b>Disclosure</b>	yes
<b>Target audience of funding/ author's interests</b>	Health insurance perspective
<b>Perspective</b>	Health insurance
<b>Indication</b>	treatment of Ventilator Associated Pneumonia
<b>Target population</b>	Insured patients by the Egyptian health care system
<b>Subgroup analysis</b>	No sub group analysis
<b>Choice of comparator</b>	Doripenem
<b>Time horizon</b>	one year
<b>Assumptions required</b>	yes
<b>Preferred analytical technique</b>	Cost-effectiveness analysis
<b>Costs to be included</b>	Total costs include costs of treatment and managing strategies according to the Egyptian current practice.
<b>Source of costs</b>	The Health insurance Hospitals
<b>Modeling</b>	Decision tree
<b>Systematic review of evidences</b>	yes
<b>Preference for effectiveness over efficacy</b>	yes
<b>Outcome measure</b>	The outcomes of the two treatments were measured in terms of quality-adjusted life-years (QALYs)
<b>Method to derive utility</b>	The method used; EQ5D from published literature
<b>Equity issues stated</b>	All lives, life years, or QALYs are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population

<b>Discounting costs</b>	No (time horizon one year )
<b>Discounting outcomes</b>	No
<b>Sensitivity analysis-parameters and range</b>	Critical component(s) in the calculation is varied through a relevant range or from worst case to best case.
<b>Sensitivity analysis-methods</b>	One-way sensitivity analysis is performed.
<b>Presenting results</b>	Imipenem-cilastatin is more costly and less effective compared to Doripenem for management of Ventilator Associated Pneumonia.
<b>Incremental analysis</b>	yes
<b>Total costs vs. effectiveness (cost/effectiveness ratio)</b>	yes

**Portability of results (Generalizability)**

The generalizability and extent to which the clinical efficacy data and the economic data are representative is identified and discussed.

• **Committee Discussion**

It is important to identify the most cost-effective treatment in patients with Ventilator Associated Pneumonia. Decision analysis is a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives and was developed to determine the cost-effectiveness of the IMI strategy, as compared to DOR in patients with Ventilator Associated Pneumonia.

The literature search was conducted in Medline, PubMed and Cochrane Library to identify relevant published English articles from January 2000 to October 2016. The decision analytical model was constructed to assess the costs and consequences associated with IMI compared with DOR. The clinical parameters were derived mainly from two sources, the first was a prospective, multicenter, parallel randomized, active-controlled, open-label study that compares doripenem versus imipenem-cilastatin on 531 patients with Ventilator Associated Pneumonia. The model structure was derived from a cost-effectiveness model of empiric doripenem compared with imipenem-cilastatin in ventilator-associated pneumonia in United States (5 - 6).

The utilities were derived from two sources; the first was a cost utility analysis that used Markov model to compare Meropenem with Imipenem - cilastatin in the treatment of severe infections in intensive care. The study elicits the utility scores from the EuroQoL (EQ-5D) social tariff for “unconscious” patients in United Kingdom (7). The second source was a cost-effectiveness model of empiric doripenem compared with imipenem-cilastatin in ventilator-associated pneumonia that used utilities estimated using time-trade off questions from 1005 patients enrolled in a five-center study of seriously ill patients (6).

Dosages of IMI and DOR were based on the Phase III trial for those drugs. The daily IMI dose was 500mg q 6 h and that for DOR 500mg q 8 h and was validated by an expert opinion.

In the base case, a three-day lag period between the onset of VAP and the availability of lower airway culture and sensitivity results was assumed, and was varied between two and four days. Patients treated with DOR testing positive for DOR-R/IMI-S PA were switched to IMI for an additional 10 days (range 7–14 days), and those treated with IMI testing positive for IMI-R/ DOR-S PA were switched to DOR for an additional 10-day course (range 7–14 days). If a specimen tested positive for a PA sensitive to the initial empiric antibiotic, this antibiotic was continued for the full 10-day course (range 7–14 days).

Direct medical costs were obtained from the health insurance hospitals in Egypt. Total costs for IMI and DOR were EGP 4646.93 and EGP 4197.58 respectively. QALYs for IMI and DOR were 0.525222843 and 0.536769973 respectively. The incremental cost-effectiveness ratio (ICER) for IMI versus DOR was L.E -

38914.30/QALY. This study showed that IMI is less effective and more costly compared to DOR in treating Ventilator Associated Pneumonia patients.

The main strengths are the use of evidence from prospective, multicenter, parallel randomized study and incorporating quality of life issues in clinical decisions. The main limitations of the study were discussed. Firstly; the study was limited to Pseudomonas aeruginosa patients as it is one of the leading pathogens in VAP. Secondly because of the paucity of long term data on VAP survivor published data on utilities in ICU so we used the utility score from the EuroQoL (EQ-5D) social tariff and it has been used in previous studies (6,7)

As in all modeling exercises, several assumptions were made in this study leading to uncertainties in the results. In this analysis, we explicitly accounted for these uncertainties by assigning confidence intervals and plausible ranges based on published sources. To assess the influences of other model structures and assumptions on the cost-effectiveness estimates, one-way sensitivity analyses of various parameters were performed and showed that probability that patients are resistant to Doripenem but sensitive to Imipenem (DOR-R / IMI-S), daily cost of imipenem-cilastatin and doripenem had the greatest impact on the results.

- **Conclusion**

Results from this study showed that IMI is less effective and more costly compared to DOR in treatment of Ventilator Associated Pneumonia. These findings will help inform health care decisions regarding the allocation of health care system resources to improve the health of the Egyptian population.

- **Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

- **PEU project team**

- **Gihan Hamdy El-sisi**, Head of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.
- **May Ahmed Samir**, Team member of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

- **References:**

1. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005; 33:2184-2193. Curti B, Bagi RB, Jana, Javeed M, et al; Renal Cell Carcinoma Overview on <http://emedicine.medscape.com/article/281340-overview>; accessed on 1st January 2014.
2. Carlet J, Ben Ali A, Chalfine A. Epidemiology and control of antibiotic resistance in the intensive care unit. *Curr Opin Infect Dis* 2004; 17:309-316.
3. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388-416.
4. Brown N, Draghi DH, Yee YC, et al. Susceptibility of *Pseudomonas aeruginosa* to doripenem and imipenem in the United States: 2006–2007 TRUST surveillance. Poster presentation at the 37th Critical Care Congress. Honolulu, HI, 2008.
5. Chastre J, Wunderink R, Prokocimer PH, et al. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: A multicenter, randomized study. *Crit-Care Med* 2008; 36, No. 4.
6. Zilberberg MD, Mody SH, et al. Cost-Effectiveness Model of Empiric Doripenem Compared with Imipenem-Cilastatin in Ventilator-Associated Pneumonia. *Surgical Infections* 2010; 11: 5.
7. Edwards SJ, Campbell HE, Plumb JM. Cost-utility analysis comparing meropenem with imipenem plus cilastatin in the treatment of severe infections in intensive care. *Eur J Health Econ* 2006; 7:72–78.
8. Shorr AF, Susla GM, Kollef MH. Linezolid for treatment of ventilator-associated pneumonia: A cost-effective alternative to vancomycin. *Crit Care Med* 2004; 32:137–143.