ORIGINAL ARTICLE

# Effectiveness and Adverse Events of Generic and Original Imipenem/Cilastatin in Hospitalized Patients: The First Multicenter Non-Inferiority Study in Thailand

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**Objective**: Imipenem/cilastatin, a broad-spectrum antibacterial, is reserved for treatment of serious infections caused by multidrug-resistant Gram-negative bacteria. The present study was aimed to compare the effectiveness and adverse events of generic and original imipenem/cilastatin.

**Materials and Methods**: A retrospective, multicenter, cohort, non-inferiority study of generic imipenem/cilastatin (Sianem®), and original imipenem/cilastatin (Tienam®) was carried on between November 2017 and September 2020. The centers included Srinagarind Hospital, Taksin Hospital, Nakornping Hospital, Nakhonpathom Hospital, and King Chulalongkorn Memorial Hospital. The clinically relevant data were retrieved from the medical records on day 3, 7, and 14 after enrollment. A sample size of 260 patients per arm was needed.

**Results**: There were 214 and 227 medical and surgical patients enrolled in generic and original imipenem/cilastatin groups, respectively. Baseline characteristics of the two groups were not significantly different. Most patients were male and elderly. Comorbidity was observed in 86.6%. The average length of hospital stay was 17 days. At day 14 after enrollment, the favorable outcome in generic and original imipenem/cilastatin groups were 83.1% and 90.0%, respectively, with no statistical difference. The mortality rates were 3.4% and 2.0% in generic and original imipenem/cilastatin groups, respectively, with no statistic difference. Serious adverse events were also not significantly different between the two groups at 0.9% and 0.4%.

**Conclusion**: The generic imipenem/cilastatin was non-inferior to the original imipenem/cilastatin in terms of effectiveness and adverse events for the treatment of serious bacterial infections in hospitalized adult patients.

**Keywords**: Effectiveness; Safety; Adverse events; Generic drug; Imipenem/cilastatin

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Imipenem is a parenteral carbapenem antibiotic. Imipenem is rapidly inactivated by renal dehydropeptidase-1 enzyme, so it must be combined with cilastatin, a renal dehydropeptidase-1 inhibitor[1-3]. It is a compact molecule that penetrates well through the outer membrane of Gram-negative bacteria. Imipenem/cilastatin is active against a broad range of bacterial pathogens including extended-spectrum beta-lactamase Gram-negative bacteria. In contrast to other β-lactam agents, imipenem exhibits a post-antibiotic effect against both Gram-positive and Gram-negative bacteria[1-3].

Imipenem/cilastatin is indicated for the treatment of many types of severe nosocomial infections caused by Gram-negative bacteria including pneumonia, intra-abdominal infection, sepsis, and febrile neutropenia[4-7].

The original formulation of imipenem/cilastatin from the innovator drug company has been used as a life-saving drug in the treatment of serious bacterial infections in Thailand for about 25 years. To date, there have been many generic formulations of imipenem/cilastatin with much lower cost in Thailand. Ideally, all of these generic

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formulations should be bioequivalent, chemically equivalent, and therapeutically equivalent to the original formulation. However, according to the regulations of Thai Food and Drug Administration, the registration of generic formulations of parenteral drugs do not need the data of bioequivalence and therapeutic equivalence in comparison with the original formulation. Randomized controlled studies regarding therapeutic equivalence between the generic and original formulations showed that the efficacy of some generic formulations was inferior to that of original formulations[8,9]. So, many clinicians are concerned that the generic formulations may not be therapeutically equivalent to the original formulation for the treatment of life-threatening infections.

The objective of the present study was to determine the effectiveness and adverse events of generic imipenem/cilastatin (Sianem®) manufactured by Siam Bheasach Co., Ltd., in comparison with original imipenem/cilastatin (Tienam®), for the treatment of serious bacterial infections in Thailand. Generic imipenem/cilastatin was prepared in a ratio of 1:1.

## Materials and Methods

A retrospective, multicenter, cohort, non-inferiority study of generic and original imipenem/cilastatin was carried on between November 2017 and September 2020 in five hospitals in Thailand including Srinagarind Hospital, Taksin Hospital, Nakornping Hospital, Nakornpathom Hospital, and King Chulalongkorn Memorial Hospital (KCMH).

The inclusion criteria included all hospitalized patients aged 18 years or older that received generic or original imipenem/cilastatin for at least 48 hours. The data were retrieved from the available medical records including demography, comorbidities, clinical data including infection site, microbiology, treatment, adverse events, and outcomes at days 3, 7, and 14 (if applicable) after enrollment.

The operational definition of all outcomes, defined based on clinical response, included 1) cure when all infection-associated symptoms were resolved, 2) improvement when at least one of all symptoms was resolved, 3) stability when no improvement nor worsening of all symptoms, 4) worsening when at least one of the symptoms was worsening, and 5) infection-associated mortality when the mortality associated directly with the infection.

The protocol was approved by the Institutional Review Board (IRB) of each hospital (KCMH: 071/58, Srinagarind Hospital: 00001189, Nakornpathom Hospital: 033/2018), and registered at the Thai Clinical Trials Registry (TCTR20210730004). A sample size of 260 patients per arm was needed based on the non-inferiority design with a type I error of 0.05, power of 80%, with expected favorable outcome from original imipenem/cilastatin treatment of 70% and the significant margin of 10%. The data were analyzed by IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). All categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were compared using unpaired t-test or Mann-Whitney U test. A p-value of less than 0.05 was considered to be statistically significant.

## Results

During the present study period, there were 441 patients from 5 hospitals including 214 patients in generic imipenem/cilastatin group and 227 patients in original imipenem/cilastatin group. Of the 441 patients, there were 150, 134, 78, 49, and 30 patients enrolled in Srinagarind Hospital, Taksin Hospital, Nakornping Hospital, Nakornpathom Hospital, and King Chulalongkorn Memorial Hospital, respectively. The baseline characteristics of the two groups were not significantly different (Table 1). Most patients were male and elderly. Comorbidity was observed in 87.4% and 85.9% of the patients in generic and original imipenem/cilastatin group, respectively. Most of them were hospitalized at the Medicine and Surgery Departments and had an average length of hospital stay of 17 days.

The infection sites and causative agents are shown in Table 2. There was no statistical difference in infection sites between the two groups except the site of lower respiratory tract (LRT) for 43 (20.1%) and 67 (29.5%) ($p=0.022$) and urinary tract for 86 (40.2%) and 55 (24.2%) ($p<0.001$) in generic and original imipenem/cilastatin groups, respectively. Causative agents between the two groups were not significantly different. Enterobacterales was the most common agent in 199 isolates (76.25%), followed by *Pseudomonas aeruginosa* at 48 (18.39%) and *Acinetobacter baumannii* at 14 (5.36%).

The dosage and duration of imipenem/cilastatin treatment are shown in Table 3. The mean dosage of imipenem was 1,794 g/day. There was statistical difference in the mean dosage of imipenem between the two groups at 1.695 and 1.893 g/day in generic and original imipenem/cilastatin groups, respectively, ($p=0.043$), since some patients in the generic

**Table 1.** Baseline characteristics of all patients

| | Generic imipenem/cilastatin (n=214) | Original imipenem/cilastatin (n=227) | p-value |
|---|---|---|---|
| Sex: male; n (%) | 132 (61.7) | 128 (56.4) | 0.259 |
| Age (year); mean [SD] | 59.4 [16.3] | 63.5 [16.8] | 0.464 |
| Weight (kg); median (IQR) | 57.0 (50.0, 65.0) | 60 (50.0, 69.1) | 0.562 |
| Ward; n (%) | | | |
| Non-intensive care unit | 15 (7.0) | 39 (17.2) | |
| Intensive care unit | 199 (93.0) | 176 (77.5) | |
| Other | 0 (0.0) | 12 (5.3) | |
| APACHE II score; median (IQR) | 13 (8, 17) | 11 (9, 18) | 0.848 |
| Length of stay before enrollment; mean [SD] | 17.5 [13.9] | 19.6 [14.9] | 0.939 |
| Charlson comorbidity index; median (IQR) | 3 (2, 5) | 3 (2, 5) | 0.415 |
| Prior use of antibiotic; n (%) | 118 (55.1) | 146 (64.3) | 0.648 |

SD=standard deviation; IQR=interquartile range

**Table 2.** Site of infection and causative agents between the 2 groups

| | Generic imipenem/cilastatin (n=214) n (%) | Original imipenem/cilastatin (n=227) n (%) | p-value |
|---|---|---|---|
| Clinically documented infection | | | |
| Site of infection | | | |
| • Urinary tract infection | 86 (40.2) | 55 (24.2) | <0.001 |
| • Lower respiratory tract infection | 43 (20.1) | 67 (29.5) | 0.022 |
| • Intraabdominal infection | 32 (15.0) | 31 (13.7) | 0.697 |
| • Bacteremia | 21 (9.8) | 16 (7.0) | 0.295 |
| • Skin and soft tissue infection | 19 (8.9) | 13 (5.7) | 0.202 |
| • Bone and joint infection | 3 (1.4) | 2 (0.9) | 0.606 |
| • Gynecologic infection | 3 (1.4) | 2 (0.9) | 0.606 |
| Microbiologically documented infection | | | |
| Causative agent | | | |
| • Enterobacterales | 91 (42.5) | 108 (47.6) | 0.286 |
| • *Pseudomonas aeruginosa* | 22 (10.3) | 26 (11.5) | 0.693 |
| • *Acinetobacter baumannii* | 8 (3.7) | 6 (2.6) | 0.512 |

**Table 3.** Dose and duration of antibiotic treatment

| | Generic imipenem/cilastatin (n=214) | Original imipenem/cilastatin (n=227) | p-value |
|---|---|---|---|
| Dose imipenem (mg/day); mean [SD] | 1,695.3 [614.0] | 1,892.7 [1,295.1] | 0.043 |
| Treatment duration (days); mean [SD] | 8.6 [5.4] | 9.0 [3.8] | 0.322 |
| Concomitant antibiotic; n (%) | 8 (3.7) | 13 (5.7) | 0.327 |

SD=standard deviation

imipenem/cilastatin group had to receive the decreased dosage of imipenem due to renal failure. There was no significant difference between the two groups in concomitant antibiotic treatment.

The clinical outcomes are shown in Table 4. At day 3 after enrollment, the favorable outcome in generic and original imipenem/cilastatin groups was 98.6% and 96.9%, respectively, with no statistical difference and an absolute difference of 1.7% (95% confidence interval (CI) –1.10 to 4.46, p=0.236). Rates of clinical worsening in generic and original imipenem/cilastatin groups was 0.9% and 3.1%, respectively with an absolute difference of 2.1% (95% CI –4.79 to 0.49, p=0.111). Mortality rate in generic and original imipenem/cilastatin groups was 0.5% and 0%, respectively with an absolute difference of 0.5% (95% CI –0.45 to 1.38, p=0.979). At day 7 after enrollment, the favorable outcome in generic and

**Table 4.** Clinical outcomes of antibiotic treatment

| | Generic imipenem/cilastatin (n=214); n (%) | Original imipenem/cilastatin (n=227); n (%) | % absolute difference | 95% CI | p-value |
|---|---|---|---|---|---|
| Clinical outcome at day 3 | | | | | |
| Favorable outcome | 211 (98.6) | 220 (96.9) | 1.7 | –1.10 to 4.46 | 0.236 |
| • Cured | 48 (22.4) | 11 (4.8) | 17.6 | –23.94 to 11.23 | <0.001 |
| • Improved | 132 (61.7) | 191 (84.1) | 22.5 | –14.19 to –30.73 | <0.001 |
| • Stable | 31 (14.5) | 18 (7.9) | 6.5 | 0.69 to 12.43 | 0.029 |
| Worse | 2 (0.9) | 7 (3.1) | 2.1 | –4.79 to 0.49 | 0.111 |
| Death due to infection | 1 (0.5) | 0 (0.0) | 0.5 | –0.45 to 1.381 | 0.979 |
| Clinical outcome at day 7 | n=174 | n=176 | | | |
| Favorable outcome | 158 (90.8) | 169 (96.0) | 5.2 | –10.39 to 0.04 | 0.078 |
| • Cured | 102 (58.6) | 77 (43.8) | 14.9 | 4.51 to 25.23 | 0.007 |
| • Improved | 49 (28.2) | 49 (27.8) | 0.3 | –9.09 to 9.73 | 1 |
| • Stable | 7 (4.0) | 43 (24.4) | 20.4 | –27.40 to –13.42 | <0.001 |
| Worse | 2 (1.1) | 5 (2.8) | 1.7 | –4.61 to 1.23 | 0.452 |
| Death due to infection | 1 (0.6) | 2 (1.1) | 0.6 | –2.49 to 1.37 | 1 |
| Discharge | 13 (7.5) | 0 (0.0) | 7.5 | 3.57 to 11.38 | <0.001 |
| Clinical outcome at day 14 | n=59 | n=50 | | | |
| Favorable outcome | 49 (83.1) | 45 (90.0) | 6.9 | –19.63 to 5.73 | 0.43 |
| • Cured | 40 (67.8) | 37 (74.0) | 6.2 | –23.23 to 10.83 | 0.616 |
| • Improved | 7 (11.9) | 8 (16.0) | 4.1 | –17.23 to 8.95 | 0.732 |
| • Stable | 2 (3.4) | 0 (0.0) | 3.4 | –1.23 to 8.01 | 0.189 |
| Worse | 3 (5.1) | 4 (8.0) | 2.9 | –12.30 to 6.46 | 0.823 |
| Death due to infection | 2 (3.4) | 1 (2.0) | 1.4 | –4.64 to 7.42 | 1 |
| Discharge | 5 (8.5) | 0 (0.0) | 8.5 | –1.37 to 15.58 | 0.962 |
| Clinical outcome at day 21 | n=8 | n=4 | | | |
| Favorable outcome | 8 (100.0) | 3 (75.0) | 25 | –17.44 to 67.44 | 0.772 |
| • Cured | 4 (50.0) | 0 (0.0) | 50 | 15.35 to 84.65 | 0.039 |
| • Improved | 1 (12.5) | 3 (75.0) | 62.5 | –110.73 to –14.27 | 0.038 |
| • Stable | 3 (37.5) | 0 (0.0) | 37.5 | –3.95 to 71.05 | 0.273 |
| Death due to infection | 0 (0.0) | 1 (25.0) | 25 | –17.44 to 67.44 | 0.773 |
| Clinical outcome at day 28 | n=3 | n=2 | | | |
| Favorable outcome | 3 (100.0) | 2 (100.0) | 0 | - | 1 |
| • Cured | 0 (0.0) | 0 (0.0) | - | - | - |
| • Improved | 1 (33.3) | 2 (100.0) | 66.7 | –120.01 to 13.32 | 0.358 |
| • Stable | 2 (66.7) | 0 (0.0) | 66.7 | –13.32 to 120.01 | 0.358 |
| Worse | 0 (0.0) | 0 (0.0) | - | - | - |
| Death due to infection | 0 (0.0) | 0 (0.0) | - | - | - |

CI=confidence interval

original imipenem/cilastatin groups was 90.8% and 96.0%, respectively, with no statistical difference and with an absolute difference of 5.2% (95% CI –10.39 to 0.04, p=0.078). At day 14 after enrollment, the favorable outcome in generic and original imipenem/cilastatin groups was 83.1% and 90.0%, respectively, with no statistical difference and with an absolute difference of 6.9% (95% CI –19.63 to 5.73, p=0.43).

Adverse events are shown in Table 5. There was no significant difference in serious adverse events between the two groups with 2 (0.9%) and 1 (0.4%) in the generic and original imipenem/cilastatin groups, respectively (p=0.962). In the generic imipenem/cilastatin group, one patient had antibiotic-associated diarrhea and one patient had drug fever. In the original imipenem/cilastatin group, one patient developed acute hepatic failure.

## Discussion

The present study has shown that generic

**Table 5.** Adverse events

| Adverse event | Generic imipenem/cilastatin (n=213) n (%) | Original imipenem/cilastatin (n=225) n (%) | % absolute difference | 95% CI | p-value |
|---|---|---|---|---|---|
| Yes | 2 (0.9) | 1 (0.4) | 0.5 | –2.05 to 1.07 | 0.961 |
| No | 211 (99.1) | 224 (99.6) | 0.5 | –1.07 to 2.05 | 0.961 |

CI=confidence interval

imipenem/cilastatin was non-inferior to original imipenem/cilastatin in therapeutic effectiveness and adverse events for the treatment of serious bacterial infections in hospitalized adult patients. The term bioequivalence implies that a generic formulation will have similar concentration and potency as the original formulation (pharmaceutical equivalence) as well as a similar pharmacokinetics (pharmacokinetic equivalence)[10]. Further on, it is usually assumed that both formulations have similar efficacy clinically (therapeutic equivalence). However, many in vivo studies showed that this assumption is wrong[11,12]. Since the regulations of Thai Food and Drug Administration do not require the data of bioequivalence and therapeutic equivalence of the generic formulations of parenteral drugs in comparison with the original formulation, many clinicians will not be confident to use generic imipenem/cilastatin for the treatment of serious bacterial infections in adult patients based on the results of the present study.

A recent study by Agudelo et al. was carried out to compare a generic product with the innovator of imipenem/cilastatin regarding pharmaceutical and pharmacokinetic equivalence in experimental animal models[12]. Surprisingly, they found that there was no therapeutic equivalence between the two products, mostly due to no pharmaceutical equivalence caused by less than 30% content of cilastatin in the generic product.

To date, there has been only one clinical study in Thailand to compare therapeutic equivalence between a generic formulation (Yungjin®) and the original formulation (Tienam®) for the treatment of bacterial infections in hospitalized patient at Siriraj Hospital[13]. The non-inferiority of therapeutic equivalence was not demonstrated since the significant margin of 95% CI of difference in primary outcomes (favorable outcomes) was more than 10%. Therefore, the present study is the first to demonstrate the non-inferiority outcomes between the generic and the original formulation of imipenem/cilastatin in Thailand.

The present study has many strengths. To the authors knowledge, it is the first multicenter non-inferiority study in Thailand comparing between a generic and original formulation of imipenem/cilastatin in the treatment of bacterial infections in hospitalized adult patients. There are all kinds of hospitals in Thailand including medical schools and provincial hospitals. They are distributed throughout Bangkok and other parts of the country including central, northern, and northeastern parts. In our study, the patients were Thai, and while they were hospitalized in all departments, they were mostly in the Medicine and Surgery Departments. There was a wide spectrum of severity of the patients enrolled ranging from mild to severe infections (APACHE II between 8 and 18). Furthermore, many infection types such as urinary tract, LRT, and intraabdominal infections were included in the present study. Hence, the generalizability could be applied to hospitalized patients with all kinds of bacterial infections as clinically indicated. Despite the limitations of retrospective design of the present study, the baseline characteristics between the two groups were well balanced. In addition, the clinical outcomes were compared up to 14 days after enrollment.

The present study has limitations. Due to retrospective design of the present study, there might be some missing data especially confounders contributing to clinical outcomes, recall or misclassification bias, and selection bias. However, the baseline characteristics and the major factors attributing to clinical outcomes of the two groups were not significantly different. The authors are confident in the results of the present study. In addition, the details of in vitro susceptibility testing were lacking due to a retrospective multicenter study. Adverse drug events of both groups were probably underestimated or overestimated due to a retrospective nature of the study.

## Conclusion

The generic imipenem/cilastatin was non-inferior to the original imipenem/cilastatin in terms of therapeutic effectiveness and safety outcomes for the treatment of serious bacterial infections in hospitalized adult patients.

## What is already known on this topic?

The original imipenem/cilastatin has been used in Thailand for the treatment of serious bacterial infections, but no study has been carried out to determine the effectiveness and adverse events of the generic imipenem/cilastatin in comparison with the original imipenem/cilastatin.

## What does this study add?

The present study was the first study to compare the generic imipenem/cilastatin with the original imipenem/cilastatin in the treatment of serious bacterial infections in hospitalized patients in Thailand. The results indicated that the generic imipenem/cilastatin was non-inferior to the original imipenem/cilastatin.

## Authors' contributions

Leelarasmee A: conceptualization, methodology, investigation, writing review and editing, supervision, and project administration; Suankratay C: conceptualization, methodology, investigation, writing original draft, supervision, and project administration.


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## Conflicts of interest

The authors declare no conflict of interests.

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