

**Questions and Answers for Health Care Providers:
Renal Dosing and Administration Recommendations for Peramivir IV**

The purpose of this document is to provide clarification regarding dosing recommendations for IV peramivir (as outlined in the Emergency Use Authorization [EUA] Fact Sheet) in patients with different degrees of renal impairment.

Q. What is the basis for the lower recommended doses of IV peramivir for patients with renal impairment (CrCl < 50 mL/min)?

A. The dosing recommendations for peramivir in patients with varying degrees of renal impairment were derived based on the results of a pharmacokinetic study in renally impaired patients conducted by BioCryst. The results of the study indicate that the systemic exposure (as assessed by the area under the plasma drug concentration-time curve, called AUC) is increased by approximately 24%, 420% and 530% in patients with mild, moderate and severe renal impairment, respectively. In patients with end stage renal disease (ESRD) receiving hemodialysis, a single dose of peramivir administered after dialysis resulted in a ~40-fold higher AUC relative to patients with normal renal function. Based on the results from the study, the following dosing recommendations were derived to target the same daily systemic exposure (AUC₀₋₂₄) as observed in patients with normal renal function receiving the full 600 mg QD dose:

Table 1: Adult Impaired Renal Function Daily Dosage Recommendations

Renal Impairment or Hemodialysis Creatinine Clearance	Daily Dose (IV)
Mild Renal Impairment CrCl 50-80 mL/min	600 mg
Moderate Renal Impairment CrCl 31-49 mL/min	150 mg
Severe Renal Impairment CrCl 10-30 mL/min	100 mg
Hemodialysis or CrCl <10 mL/min	15 mg

† The dose should be adjusted in patients with impaired renal function (CrCl less than 50 mL/min).

On dialysis days, Peramivir IV should be administered after hemodialysis is Completed

Q. What additional data were used to derive dosing in renally impaired patients?

A. To further confirm the similarity in systemic exposures between patients with different degrees of renal impairment and patients with normal renal function, computer simulations were conducted to predict the maximum concentration at steady-state (C_{maxss}), minimum concentration at steady-state (C_{minss}) and the AUC within one dosing interval at steady-state (AUC_{ss}) at the dosing regimens outlined in Table 1. The results (plasma concentrations over time) of these simulations indicate that systemic exposures and average steady state concentrations at the various proposed dosing regimens are expected to be similar to the systemic exposures and average steady state concentrations after administration of 600 mg QD to subjects with normal renal function. In other words, although the peramivir daily dose is lower for each level of renal

impairment, the systemic exposure and average concentrations are expected to be similar to that of a patient with normal renal function given the 600 mg QD dose.

The minimum concentrations at steady state ($C_{\min,ss}$) for the various proposed renal impairment dosing regimens are expected to be higher (based on the simulations) than the C_{\min} observed after administration of 8 mg/kg (~600 mg for a 70 kg adult) to healthy subjects with normal renal function (~30 ng/mL). There are no data to indicate whether a higher C_{\min} will be associated with improved efficacy.

Q. Is a loading dose needed for patients with renal impairment?

A. No, there are no data that would indicate a loading dose is needed for patients with renal impairment receiving the doses outlined above in Table 1. The simulations of the proposed dosing regimens suggest minimal accumulation of peramivir after repeat dosing. The AUC on Day 1 is expected to be similar to the AUC on Day 5 for all degrees of renal impairment, as well as for patients with normal renal function following administration of the full 600 mg QD dose. All patients (regardless of degree of renal impairment) are expected to achieve steady-state exposures starting on Day 1. Therefore, the use of a loading dose will not provide additional benefit in terms of reaching steady-state plasma levels of peramivir faster.

Q. If the recommended renal impairment doses result in a lower C_{\max} , than the C_{\max} expected after administration of peramivir 600 mg QD to subjects with normal renal function, then why is this considered acceptable?

A. The recommended renal impairment doses will result in a lower C_{\max} than the C_{\max} expected after administration of peramivir 600 mg QD to subjects with normal renal function. However, this is considered acceptable for the following reasons:

- There are no data to suggest that a higher C_{\max} is associated with greater efficacy for peramivir.
- There are insufficient safety data available for the higher systemic exposures expected after a loading dose in a patient with renal impairment. If a dose higher than the proposed dose is used (for any degree of renal impairment) in order to target the same C_{\max} as observed in patients with normal renal function given 600 mg QD, the systemic exposures (AUC) will be several fold higher than the systemic exposures for which safety data are available.

Q. What is the recommended dose for a patient on continuous renal replacement therapy?

A. Currently there are no data to guide specific dosing recommendations for Peramivir IV in patients undergoing one of the various types of continuous renal replacement therapy (CRRT)(i.e. continuous venovenous hemofiltration, venovenous hemodialysis and venovenous hemodiafiltration). Dosing should be based on clinical knowledge of the patient's current creatinine clearance combined with the expected clearance due to the type of CRRT modality and follow the current dosing recommendations by creatinine clearance in the Fact Sheet for Health Care Providers.

Q. Can I measure plasma concentrations of peramivir in my patient for therapeutic drug monitoring (TDM)?

A. No, at this time it is not possible to measure plasma concentrations of peramivir in a timely enough manner to impact clinical care. Further, it is unclear which timepoint(s) should be measured and what the therapeutic target(s) are, due to the lack of exposure-response data for peramivir.

Q. Can other intravenous medications be administered with intravenous peramivir?

A. The compatibility of peramivir injection with IV solutions and medications other than Sodium Chloride Injection, USP is not known. The clinician needs to use clinical judgment regarding administration of concomitant medications during infusion based on the individual patient's medical situation.