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

The purpose of this document is to provide additional clarification to the existing information and summarize new information related to the dosing recommendations for Peramivir IV in patients with end stage renal disease (ESRD) and patients receiving continuous renal replacement therapy (CRRT).

Q1. What are the latest revisions to the Peramivir IV Fact Sheet for Health Care Providers related to the dosing recommendations for Peramivir IV in patients with renal impairment?

A. The latest updates to the dosing recommendations in the Fact Sheet for Health Care Providers for Peramivir IV are described below:

Adult and Pediatric Patients:

- Revision of Dosing in Patients with End Stage Renal Disease (ESRD) on Intermittent Hemodialysis (HD)
- New Dosing Information for Patients with Creatinine Clearance (CrCl) less than 10 mL/minute and NOT on Intermittent Hemodialysis (HD) or Continuous Renal Replacement Therapy (CRRT)
- New Dosing Information for Patients Undergoing Continuous Renal Replacement Therapy (CRRT)

Q2. What is the basis for the current recommended doses of Peramivir IV for patients with renal impairment (CrCl < 50 mL/min)?

A. The Peramivir IV dosing recommendations in patients with varying degrees of renal impairment were based on the results of a pharmacokinetic study in patients with renal impairment conducted by BioCryst. The results of the study indicate that the systemic exposure of peramivir (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 IV administered after dialysis resulted in an ~40-fold higher $AUC_{0-\infty}$ relative to patients with normal renal function.

Based on the results from the study, the following dosing recommendations were developed to target the same daily systemic exposure (AUC_{0-24}) as observed in adult patients with normal renal function receiving the full 600 mg QD dose:

Fact Sheet Table 1: Adult Impaired Renal Function Daily Dosage Recommendations

Creatinine Clearance (CrCL[1]) or Estimated Clearance (CL_{CRRT}[2] + Residual Renal CL)	**Dose (IV)**
Mild Renal Impairment 50-80 mL/min	600 mg QD
Moderate Renal Impairment 31-49 mL/min	150 mg QD
Severe Renal Impairment 10-30 mL/min	100 mg QD
End Stage Renal Disease (ESRD) on Intermittent Hemodialysis (HD)	100 mg on Day 1, then 100 mg given 2 hrs after each HD session **on dialysis days only**

[1] Calculated using Cockcroft and Gault equation, when serum creatinine represents a steady state of renal function

[2] Calculated using equation applicable to type of CRRT. See equations under Calculation of CRRT Clearance for Various Types of CRRT.

. **Note:** In adult patients with renal failure with CrCl <10 mL/min who are **not on intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT)**, the recommended dose of Peramivir IV is 100 mg on Day 1 of dosing, followed by 15 mg QD thereafter.

Q3. What additional data were used to derive dosing for patients with renal impairment?

A. Simulations were used to further evaluate the similarity in systemic exposures between patients with different degrees of renal impairment and patients with normal renal function. The simulations predicted 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 Fact Sheet Table 1.

The simulation results (plasma concentrations over time) 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 observed after administration of 600 mg QD to subjects with normal renal function.

The minimum concentrations at steady state (C_{minss}) for the various proposed dosing regimens in Fact Sheet Table 1 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.

Q4. Is a loading dose needed for patients with renal impairment?

A. There are no data that indicate a loading dose is needed for patients with mild, moderate or severe renal impairment or for patients with end stage renal disease (ESRD) on intermittent hemodialysis receiving the doses outlined in Fact Sheet Table 1. The simulations, using 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 patients with mild, moderate or severe renal impairment, as well as for adult patients with normal renal function following administration of the full 600 mg QD dose. Therefore, administering a loading dose is not expected to provide significant benefit in achieving steady-state plasma concentrations in these patients.

A loading dose is recommended only for patients with a creatinine clearance <10 ml/min who are **NOT** on intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT). Please see Q8 for additional details.

Q5. Why is it considered acceptable that the recommended doses for patients with renal impairment result in a lower C_{max}, compared to the C_{max} observed in patients with normal renal function after administration of Peramivir IV 600 mg QD?

A. It is considered acceptable that the doses for patients with renal impairment will result in a lower C_{max} compared to the C_{max} observed after administration of Peramivir IV 600 mg QD to adult patients with normal renal function for the following reasons:

- There are no data to suggest that a higher C_{max} for peramivir is associated with greater efficacy.
- There are insufficient safety data available for the higher systemic exposures expected after a loading dose in a patient with mild, moderate, or severe renal impairment. Therefore, 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 adult 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.

Q6. What is the recommended dose of Peramivir IV for an adult patient with ESRD on intermittent HD?

A. The recommended dose is 100 mg on Day 1 followed by 100 mg given 2 hours after each HD session **on dialysis days only**. Based on simulations, this dose is predicted to provide comparable peramivir exposure (AUC_{0-24}) to that observed in patients with normal renal function (C_{max} will be lower and C_{min} will be higher, see Fact Sheet Table 5 and Fact Sheet Figure 1 below). The AUC_{0-24} values over the dosing period are predicted to be relatively stable for this dosing regimen (range 93,400 – 106,000 ng·h/mL). The simulations were performed assuming a 4-hour HD session and a Q48h HD schedule.

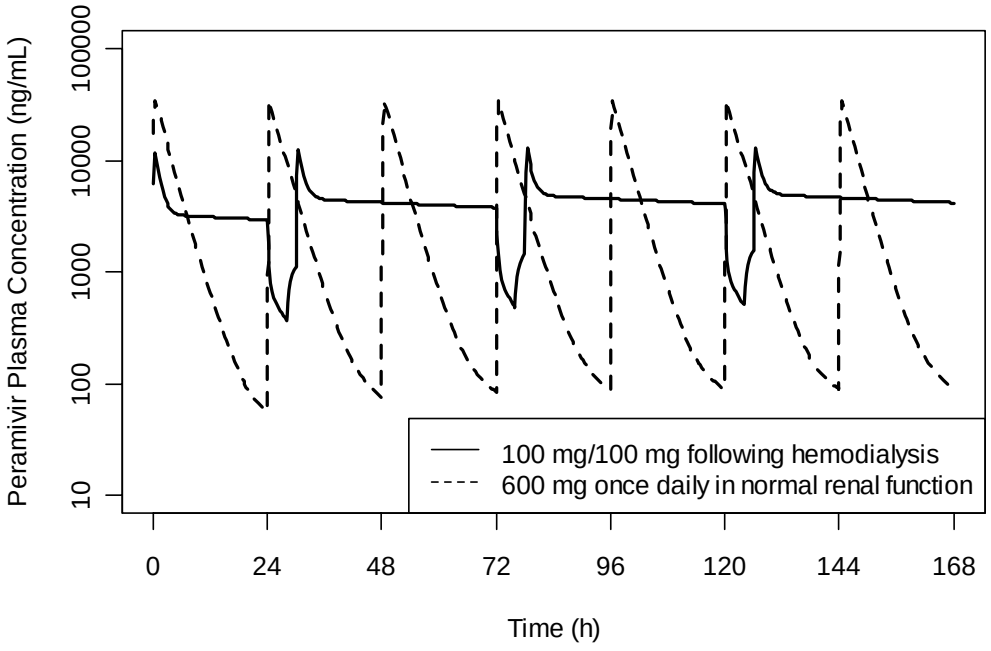
However, the same dosing recommendation (100 mg after each HD session) is appropriate if HD is administered on two consecutive days.

Fact Sheet Table 5. Predicted PK parameters in patients with ESRD on intermittent HD

	Normal Renal Function (600 mg QD)	Intermittent HD (100 mg on Day 1, then 100 mg Given 2 Hrs After Each HD Session)
AUC_{0-24} (average[1]) (ng·h/mL)	107,000	98,000
C_{max} (ng/mL)[2]	34,100	13,100
C_{min} (ng/mL)[2]	56	370

Note: Simulations were performed assuming a 4-hour HD session, every 48 hours. Simulations were performed for a 7-day dosing duration.
[1] Average AUC_{0-24} is the average of all AUC_{0-24} values predicted for the 7-day treatment duration.
[2] C_{max} is the highest predicted C_{max} and C_{min} is the lowest predicted C_{min} for the simulated dosing period.

Fact Sheet Figure 1. Predicted Peramivir Concentration in patients with ESRD on intermittent HD



Q7. Why has the dose of Peramivir IV for adult patients with ESRD on intermittent HD changed from what was originally recommended for these patients?

A. The dose originally recommended for patients with ESRD on intermittent HD was 15 mg once daily. This dose was based on an ~40-fold higher $AUC_{0-\infty}$ of peramivir after

administration of a single dose of Peramivir IV to patients on intermittent HD relative to patients with normal renal function. However, the results of additional simulations have shown that the 15 mg once daily dose does not fully account for the loss of peramivir during the hemodialysis session. Therefore, the dose has been revised in order to fully account for the loss of peramivir during the hemodialysis session and provide systemic exposures similar to the systemic exposures after administration of 600 mg once daily in an adult patient with normal renal function. The revised dose is 100 mg on Day 1 followed by 100 mg given 2 hours after each hemodialysis session **on dialysis days only.** The simulations were performed assuming a 4-hour HD session and a Q48h HD schedule. However, the same dosing recommendation (100 mg after each HD session) is appropriate if HD is administered on two consecutive days. The predicted concentrations for the recommended dose are shown above in Fact Sheet Table 5 and Fact Sheet Figure 1.

Q8. What is the recommended dose of Peramivir IV for an adult patient with CrCl <10 ml/min but NOT on intermittent HD or CRRT?

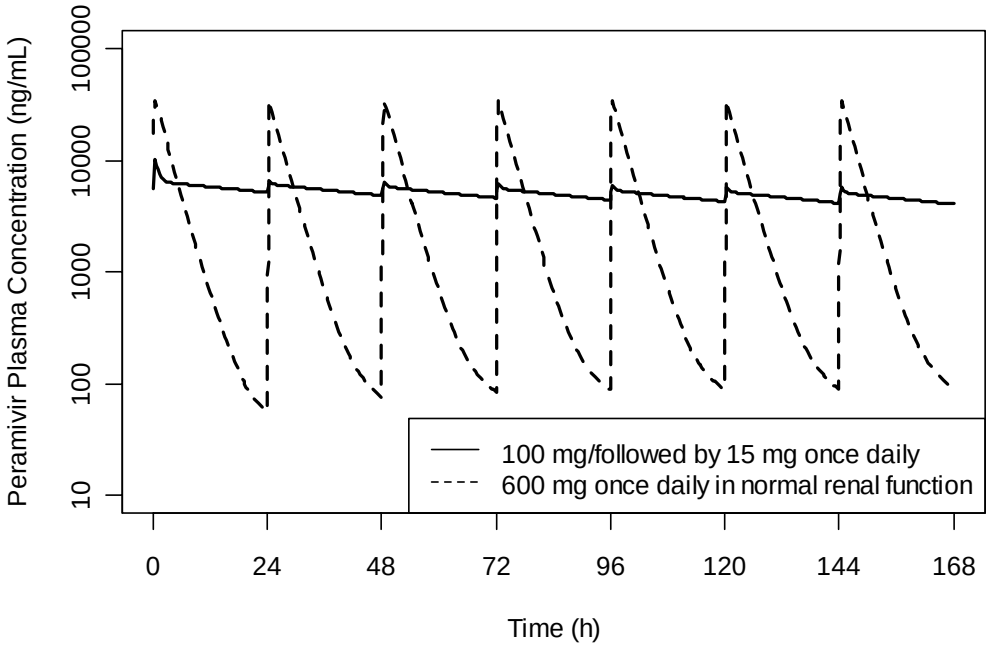
A. The recommended dose is 100 mg on Day 1 followed by 15 mg once daily thereafter. This dosing regimen is predicted to provide average $AUC_{0\text{-}24}$ values similar to adult patients with normal renal function receiving 600 mg QD. The peramivir C_{max} and C_{min} for this dosing regimen are predicted to be lower and higher, respectively, relative to patients with normal renal function (see Fact Sheet Table 6 and Fact Sheet Figure 2 below). The initial 100 mg dose on Day 1 is intended to bring peramivir concentrations to levels similar to those in patients with normal renal function beginning on Day 1.

Fact Sheet Table 6. Predicted PK parameters in patients with CrCl <10 mL/min and NOT on intermittent HD or CRRT

	Normal Renal Function	**CrCl < 10 mL/min and NOT on intermittent HD or CRRT**
	600 mg QD	**100 mg on Day 1, followed by 15 mg QD**
$AUC_{0\text{-}24}$ (average)[1] (ng·h/mL)	107,000	122,000
$AUC_{0\text{-}24}$ (Day 1) (ng·h/mL)	106,000	142,000
C_{max}[2] (ng/mL)	34,100	10,300
C_{min}[2] (ng/mL)	56	4,060

Note: Simulations were performed assuming a 7-day dosing duration.
[1] Average $AUC_{0\text{-}24}$ is the average of all $AUC_{0\text{-}24}$ values predicted for the 7-day treatment duration.
[2] C_{max} is the highest predicted C_{max} and C_{min} is the lowest predicted C_{min} for the simulated dosing period

Fact Sheet Figure 2. Predicted Peramivir IV Concentration in Patients with CrCL < 10 mL/min and NOT on Intermittent HD or CRRT



Q9. What is the recommended dose of Peramivir IV for an adult patient on CRRT?

A. Very limited data available for Peramivir IV in the setting of CVVH and CVVHD indicate peramivir is efficiently cleared by CRRT. Ultrafiltrate concentrations from a single adult patient on CVVH revealed a high sieving coefficient (~80%), consistent with Peramivir's low protein binding (<30%).

The following steps should be followed sequentially to determine the recommended dose of Peramivir IV for a patient on CRRT. Consultation with the health care provider managing the CRRT is recommended.

Step 1: Depending on the type of CRRT, estimate the CRRT clearance (CL_{CRRT}) using the following equations:

Calculation of CRRT Clearance for Various Types of CRRT

Type of CRRT	CL_{CRRT}
For slow continuous ultrafiltration (SCUF) or continuous arterio-venous hemofiltration (CAVH) or continuous veno-venous hemofiltration (CVVH):	$CL_{CRRT} = Q_f$
For continuous arterio-venous hemodialysis (CAVHD) or continuous veno-venous hemodialysis (CVVHD):	$CL_{CRRT} = Q_d$
For continuous arterio-venous hemodiafiltration (CAVHDF) and continuous veno-venous hemodiafiltration (CVVHDF):	$CL_{CRRT} = Q_f + Q_d$

Where Q_f = ultrafiltration rate (mL/min) and Q_d = dialysate flow rate (mL/min)

It should be noted that the equations above are based on several assumptions about peramivir, including low or negligible protein binding (fraction unbound, f_u=1) and high sieving coefficient (SC=100%). These assumptions may result in over-estimation of clearance depending on actual protein binding or sieving coefficient. For CRRT methods with a diffusive component (CVVHD and CAVHD), the equations do not account for dialysate saturation, which may result in a higher CL_{CRRT} estimate than is actually observed.

Step 2: Determine the patient's residual renal clearance while on CRRT (if any) and add this residual renal clearance to the patient's CRRT clearance (CL_{CRRT}) determined in step 1. The sum of residual renal clearance and CL_{CRRT} provide an estimate of the patient's total clearance. Consultation with the health care provider managing the CRRT is recommended to most accurately estimate the patient's total clearance, including CRRT clearance, on a case-by-case basis.

Step 3: Using the estimate of the patient's total clearance computed in step 2, refer to Fact Sheet Table 1 ("Adult Impaired Renal Function Dosage Recommendations") to determine the dose of Peramivir IV for the patient. Dose modifications should be made, as appropriate, for changes in patient renal function, changes to ultrafiltrate or dialysate flow rate, or initiation, discontinuation or changes to CRRT.

Q10. What is the recommended dose of Peramivir IV for a pediatric patient with ESRD on intermitted HD?

A. The following table, Fact Sheet Table 3 shows the dosing recommendations for pediatric patients with impaired renal function. The highlighted column entitled, "ESRD (< 10 ml/min/1.73m^2) on Intermittent Hemodialysis" shows the recommended dose for a pediatric patient with ESRD on intermittent HD.

Fact Sheet Table 3. Pediatric Impaired Renal Function Dosage Recommendations

Age	**Creatinine Clearance (CrCl[1]) or Estimated Clearance (CL_{CRRT} [2]+ Residual Renal CL)**				
	50-80 mL/min/1.73 m^2	**31-49 mL/min/1.73 m^2**	**10-30 mL/min/1.73m^2**	**< 10 mL/min/1.73 m^2 and NOT on Intermittent HD or CRRT**	**ESRD (<10 mL/min/1.73 m^2) on Intermittent Hemodialysis**
Birth through 30 days	6 mg/kg QD	1.5 mg/kg QD	1 mg/kg QD	1 mg/kg on Day 1, then 0.15 mg/kg QD	1 mg/kg on Day 1, then 1 mg/kg given 2 hrs after each HD session **on dialysis days only**

31 Days through 90 Days	8 mg/kg QD	2 mg/kg QD	1.3 mg/kg QD	1.3 mg/kg on Day 1, then 0.2 mg/kg QD	1.3 mg/kg on Day 1, then 1.3 mg/kg given 2 hrs after each HD session **on dialysis days only**
91 Days through 180 Days	10 mg/kg QD	2.5 mg/kg QD	1.6 mg/kg QD	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session **on dialysis days only**
181 Days through 5 Years	12 mg/kg QD	3.0 mg/kg QD	1.9 mg/kg QD	1.9 mg/kg on Day 1, then 0.3 mg/kg QD	1.9 mg/kg on Day 1, then 1.9 mg/kg given 2 hrs after each HD session **on dialysis days only**
6 Years through 17 Years	10 mg/kg QD	2.5 mg/kg QD	1.6 mg/kg QD	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session **on dialysis days only**

[1] Calculated using Schwartz equation when serum creatinine represents a steady state of renal function.
[2] Calculated using equation applicable to type of CRRT. See equations under Calculation of CRRT Clearance for Various Types of CRRT.

Q11. Why has the dose of Peramivir IV for pediatric patients with ESRD on intermittent HD changed from what was originally recommended for these patients?

A. For a given degree of renal impairment, the dose recommended for a pediatric patient with normal renal function was reduced by the same magnitude that the adult dose was reduced. The recommended dose for adult patients was revised based on simulations that predict a dose of 100 mg (1/6th the full dose) given on Day 1, followed by 100 mg after each HD session results in similar exposure to adults with normal renal function receiving the full 600 mg dose (as described above in Q6). Therefore, the same modification in dose is recommended for the various pediatric age groups (1/6th the full dose given on Day 1 and after each HD session thereafter). This is the last column in Fact Sheet Table 3.

Q12. What is the recommended dose for a pediatric patient with ESRD and NOT on intermittent HD or CRRT based on?

A. The recommended doses of Peramivir IV for pediatric patients with ESRD and NOT on intermittent HD or CRRT were based on the same factor by which the dose is reduced in adult patients. The recommended dose for adults was based on computer simulations that predict a dose of 100 mg (1/6th the full dose) given on Day 1, followed by 15 mg QD

in patients with a CrCl < 10 mL/min and NOT on intermittent HD or CRRT is expected to result in similar exposure to patients with normal renal function. Therefore, the same reduction in dose was made for the various pediatric age groups ($1/6^{th}$ the full dose on Day 1, followed by $1/40^{th}$ the dose given QD thereafter). This is the 2^{nd} to last column in Fact Sheet Table 3, "< 10 ml/min/1.73m^2 and NOT on intermittent HD or CRRT" and is shown highlighted below.

Fact Sheet Table 3. Pediatric Impaired Renal Function Dosage Recommendations

Age	Creatinine Clearance (CrCl[1]) or Estimated Clearance (CL_{CRRT} [2]+ Residual Renal CL)				
	50-80 mL/min/1.73 m^2	**31-49 mL/min/1.73 m^2**	**10-30 mL/min/1.73m^2**	**< 10 mL/min/1.73 m^2 and NOT on Intermittent HD or CRRT**	**ESRD (<10 mL/min/ 1.73 m^2) on Intermittent Hemodialysis**
Birth through 30 days	6 mg/kg QD	1.5 mg/kg QD	1 mg/kg QD	1 mg/kg on Day 1, then 0.15 mg/kg QD	1 mg/kg on Day 1, then 1 mg/kg given 2 hrs after each HD session **on dialysis days only**
31 Days through 90 Days	8 mg/kg QD	2 mg/kg QD	1.3 mg/kg QD	1.3 mg/kg on Day 1, then 0.2 mg/kg QD	1.3 mg/kg on Day 1, then 1.3 mg/kg given 2 hrs after each HD session **on dialysis days only**
91 Days through 180 Days	10 mg/kg QD	2.5 mg/kg QD	1.6 mg/kg QD	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session **on dialysis days only**
181 Days through 5 Years	12 mg/kg QD	3.0 mg/kg QD	1.9 mg/kg QD	1.9 mg/kg on Day 1, then 0.3 mg/kg QD	1.9 mg/kg on Day 1, then 1.9 mg/kg given 2 hrs after each HD session **on dialysis days only**
6 Years through 17 Years	10 mg/kg QD	2.5 mg/kg QD	1.6 mg/kg QD	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session **on dialysis days only**

[1] Calculated using Schwartz equation when serum creatinine represents a steady state of renal function.
[2] Calculated using equation applicable to type of CRRT. See equations under Calculation of CRRT Clearance for Various Types of CRRT.

Q13. Is there information available regarding the use of Peramivir IV in patients undergoing extracorporeal membrane oxygenation (ECMO)?

A. There is no information available on peramivir exposure or pharmacokinetics specific to patients receiving extracorporeal membrane oxygenation (ECMO).

Q14. Can I measure plasma concentrations of Peramivir IV in a 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.

Q15. Can other intravenous medications be administered with Peramivir IV?

A. The compatibility of Peramivir injection with IV solutions and medications other than Sodium Chloride Injection, USP is not known. The clinician should use clinical judgment regarding administration of concomitant medications during infusion based on the individual patient's medical situation. To the extent possible, Peramivir IV should not be administered simultaneously with another intravenous medication.

Heparin Lock

Before infusion of Peramivir IV via a heparin lock, the port should be flushed with 3-5 mLs of sterile saline. After the infusion of Peramivir IV is complete, the port should be flushed again with sterile saline and then heparin can be added to maintain patency of this catheter.

Single or Multilumen Catheter

If other medications are also administered via a single lumen catheter or a single lumen of a multilumen catheter, at least 10 mLs of saline should be administered between the infusion of any other medication and the administration of Peramivir IV to assure that all medication is flushed from the catheter tubing before Peramivir IV is administered.

Peramivir IV may be piggybacked into an existing saline infusion line. Where possible, the saline infusion rate should be reduced to assure that Peramivir IV is infused over 30 minutes for adults and over 60 minutes for pediatric patients.